IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Unraveling "Alzheimer's Disease" A Comprehensive Review

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ABSTRACT

Alzheimer's disease (AD) is a common neurodegenerative disease characterized by progressive cognitive decline and memory loss. Although the exact etiology of AD is unknown, extensive research has revealed an important role for genetic factors in its pathogenesis. This comprehensive review aims to provide an overview of the genetic basis of Alzheimer's disease and identify key genes involved in disease susceptibility. Several genes have been identified that contribute to the development of AD. The amyloid precursor protein (APP) gene, located on chromosome 21, is associated with the production of the abnormal amyloid beta protein that is a hallmark of AD pathology. Mutations in the gene Presenilin 1 (PSEN1) on chromosome 14 and Presenilin 2 (PSEN2) on chromosome 1 cause early-onset familial Alzheimer's disease by affecting APP processing and beta-amyloid production. Another important genetic factor is the Apolipoprotein E (APOE) gene located on chromosome 19. The APOE ε4 allele is the best-known genetic risk factor for late-onset Alzheimer's disease. Its presence increases susceptibility to AD, which has a dose-dependent effect. It is important to note that genetic risk factors are not segregated. Environmental factors, lifestyle, and general health play an important role in the onset and progression of the disease. Understanding the interplay between genetic and environmental factors is critical to elucidating the complexity of AD. This review highlights the need for further research to elucidate the complex mechanisms by which these genetic factors contribute to AD pathogenesis. Studying interactions between genes and environmental factors can provide valuable insights into potential therapeutic targets and prevention strategies.

KEYWORDS: Alzheimer's disease, genetics, amyloid precursor protein, presenilin, pathogenesis.

INTRODUCTION

Alzheimer's disease is characterized by a progressive cognitive decline, which usually begins with a decrease in the ability to form recent memories, but inevitably affects all intellectual functions and leads to complete dependence on the basic functions of daily life and premature death. Pathological manifestations of Alzheimer's disease include diffuse and neurogenic extracellular amyloid plaques and reactive microgliosis, dystrophic neurites and intracellular neurofibrillary tangles with loss of neurons and synapses (Serrano-Pozo et al. 2011). Although these pathological lesions do not fully explain the clinical features of the disease, it has been suggested that changes in the production and processing of amyloid b protein may be a major factor in pathogenesis. The causes underlying these multifaceted changes are unclear, but aging, genetic and non-genetic predisposition factors are believed to play a role. Alzheimer's disease is the most common cause of dementia in Western societies. About 5.5 million people are affected in the United States and 24 million worldwide. Rapid population aging in both developed and developing countries is expected to double the incidence every 20 years by 2040. The magnitude of the projected increase in the aging population is substantial and will represent a significant burden on public health in the coming years.

DEFINITIONS & CRITERIA [1]

In 1984, representatives of the National Institute of Neurological and Communication Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) developed a unified set of criteria to allow clinicians and researchers to maintain diagnostic consistency. This includes aspects of the medical history, clinical examination, neuropsychological examination, and laboratory assessment (McCann et al. 1984). These criteria have been highly reliable and valid for the diagnosis of AD for the past 30 years (Galasco et al. 1994; Lim et al. 1999). The criteria were developed to accurately correlate clinical symptoms with postmortem neuropathological manifestations. For autopsy-confirmed disease, for a typical clinical syndrome without possible interfering problems, and for complicated diagnoses of conditions that could contribute to dementia, confidence levels were set to be considered definitive. These criteria helped to estimate the prevalence and incidence of clinically diagnosed probable and probable Alzheimer's disease. The NINCDS-ADRDA criteria have recently been updated (McKhann et al. 2011). Neuropsychological assessment, brain imaging, and significant advances in the neuropathological, biochemical, and genetic understanding of this disease were deemed necessary for adjustment. The prevalence of the AD phenotype in the community is higher than previously thought. For example, neuropathological changes may precede clinical dementia by 10 years or more. Increased use of brain imaging and CSF biomarkers may increase both diagnostic specificity and sensitivity and should be considered in updated diagnostic criteria, particularly when used in clinical trials. It is becoming increasingly clear that cerebrovascular disease coexists with Alzheimer's disease to varying degrees, further contributing to cognitive and physical dysfunction. The newly proposed set of criteria is like the 1984 NINCDS-ADRDA criteria, but differs from the update by including changes in recognition of amnestic and non-amnestic symptoms and in many other cognitive domains. Cerebrovascular disease is also now recognized as contributing to dementia, which is defined as the onset or worsening of cognitive impairment, the presence of multiple or widespread infarcts, or a history of stroke temporally associated with severe high-intensity white matter lesions on MRI. Thus, the presence of significant cerebrovascular pathology reduces the reliability of the clinical diagnosis of AD. Hallucinations, delusions, parkinsonian-like motor symptoms, and associated findings may indicate dementia with Lewy bodies or other forms of dementia (Tarawneh and Holtzman 2011; Weintraub et al. 2011).

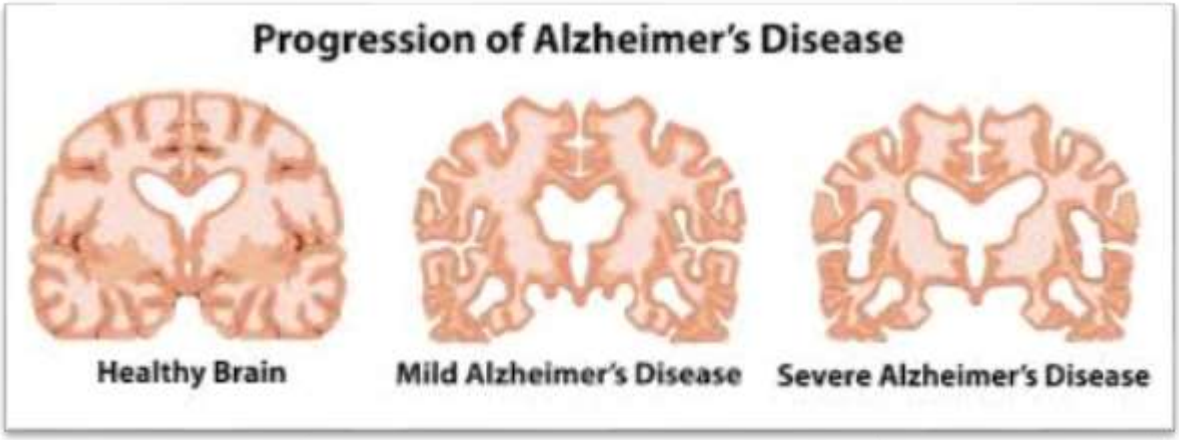

Fig 1: Progression of Alzheimer's Disease

UNDERSTANDING THE BIOLOGY OF ALZHEIMER'S DISEASE

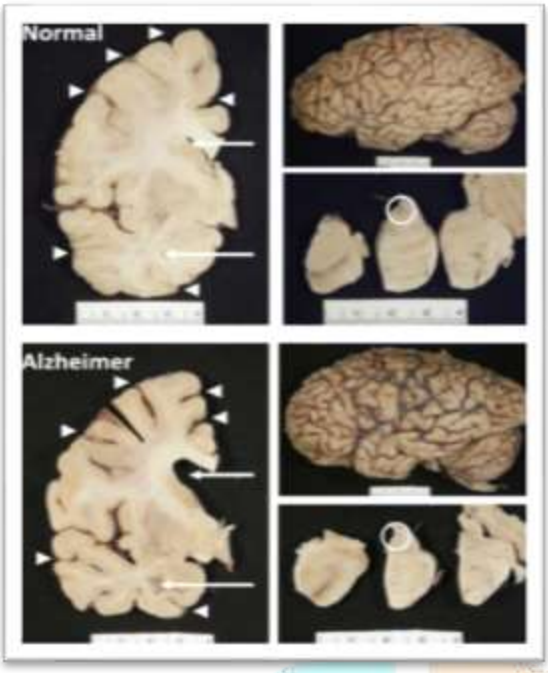

Fig 2: Normal Vs Alzheimer Brain

Importantly, imaging has an important role to play in improving our understanding of this disease (or diseases). Uniquely, lifetime imaging can reveal the location of AD effects in the brain. Imaging combined with this topographical information can quantify different aspects of AD pathology and assess how they relate to each other and how they change over time. Clinical correlates of these changes and their association with other biomarkers and prognosis can be explored. Finally, the role of imaging in advancing our understanding of Alzheimer's biology is central to all its applications and is a topic we will discuss in the next section of this article

EPIDEMIOLOGY

AD is the most common neurodegenerative disorder and the sixth leading cause of death in the United States.[2] Although there is increasing evidence that AD pathology begins to be confined to the brain in middle age, the first clinical symptoms usually appear after age 65. [3,4]

The prevalence of AD is increasing rapidly, with the proportion of people aged 65 and over increasing faster than any other age group in the world's population. Between 1997 and 2050, the elderly population, defined as those aged 65 and over, will increase from 63 to 137 million in the Americas, from 18 to 38 million in Africa, and from 113 to 100 million in Europe. It will increase to 70 million. million, from 172 million to 435 million. in Asia.[5] The US National Dataset on Aging, Demographics, and Memory Study (ADAMS) estimated that 14% of the US population over the age of 71 has dementia. Alzheimer's dementia accounted for 70% of dementia cases across the age spectrum in this cohort.[6] In a subsequent publication, ADAMS researchers reported that an additional 22% (or 5.4 million Americans) over the age of 71 had cognitive impairment without overt dementia.[7]

Although age is the biggest risk factor for developing Alzheimer's disease, age alone is not enough to cause Alzheimer's disease. Other important risk factors include the presence of one or more apolipoprotein E4 alleles (APOE4), low education and occupation, family history of AD, moderate or severe traumatic brain injury, and cardiovascular risk factors. Genes control AD prevalence. Two-thirds of all patients diagnosed with AD are women.[8] According to ADAMS, only 16% of women and 11% of men will develop dementia after age 71. While it is true that women live longer than men, this alone does not explain the difference. Genetic, hormonal, and social factors (for example, lower levels of education and occupation in women between the ages of 70 and 80 compared to men) also play a role. Racial differences in the prevalence of Alzheimer's disease have also been reported. Older African Americans and Hispanics have a higher prevalence of AD than older whites, in part due to lower educational attainment and a higher prevalence of cardiovascular disease, although other genetic and social factors may play a role, also a role. Clinical diagnosis and staging of patients with Alzheimer's disease.[8]

CLINICAL ASPECTS

Advertising is the most common type of dementia, good for all dementia. [9-12] As the disease develops, car dysfunction, such as parkinsonism, myoclonus, spastic par apars and attacks, as well as neurological and neuropsychiatric symptoms. The correct use of critical clinical control critics and genetic tests in phenotype.[13]

The diagnostic criteria AD is based on psychological disorders, the 4th edition, the 4th edition and the national neurological disorders, the communicative disorders and based on the diagnostic and statistical instructions based on the working group of the working group. [15,16] Real diagnosis. Determination of pathogenic mutations only after the autopsy of the symptomatic individual in the advertisement (National Anti-Guard Institute) from advertising. [17,18] The risk of developing advertising is related to genetic and age factors, but the level of gender, education, and the history of head injury, including investigation and influence. [19-21]
In general, the members of the population constitute about 10-12% of the development of advertising throughout life. The exact cost of risks is only available for people with family history who meet the e-mail and dominant advertising. Biomarker research for AD is ongoing worldwide for use in diagnosis, prediction of disease progression, pre-symptomatic predictive testing, and clinical trials. Results indicate that beta-amyloid peptide (Aβ1-42) in cerebrospinal fluid (CSF), total tau, and phosphorylated tau levels were significantly correlated with disease status. minor cognitive deficit.[22-24] Neuroimaging using magnetic resonance imaging, positron emission tomography, and Pittsburgh Compound B positron emission tomography improves the efficacy of cerebrospinal fluid markers.[25] The lack of use of markers has led to variability in measurements between laboratories and within studies [24-26] Currently, some clinicians use CSF biomarkers for the differential diagnosis of dementia, indicating that patients are susceptible to after AD. instead of other forms of dementia. Care should be taken when interpreting these tests, as the results are inconclusive. Similarly, these test results cannot be used to predict the transition time from MCI to AD or as a definitive diagnostic test compared to other APOE genotypes shows that the probability of AD is higher. [24,28]

Currently, AD treatment aims to slow disease progression through two main processes: cholinesterase inhibitors and N-methyl-D-aspartic acid receptor antagonists. Some studies suggest that a lifestyle that improves cardiovascular health may be beneficial in reducing the risk of AD or delaying the age of onset. [29,30] In addition, nonpharmacological treatments (environmental modification and caregiver training) may be effective in managing behavioral problems associated with AD, such as depression, agitation/aggression, rhythm, and sleep disturbances. [31-33]

GENETIC ASPECTS [34]

Alzheimer's disease is a complex and multifactorial neurodegenerative disease caused by a combination of genetic and environmental factors. Although the exact cause of Alzheimer's disease is not fully understood, genetic factors play a role in its pathogenesis. Several genes have been identified that are associated with an increased risk of developing Alzheimer's disease. Some of the major genes involved are:

1. Amyloid precursor protein (APP) gene: Mutations in the APP gene, located on chromosome 21, can produce an abnormal form of amyloid beta protein, a major component of the amyloid plaques in the brains of Alzheimer's patients.

2. Presenilin 1 gene (PSEN1): Mutations in the PSEN1 gene, located on chromosome 14, are associated with early-onset familial Alzheimer's disease. This gene provides instructions to produce proteins involved in APP processing and beta amyloid production.

3. Presenilin 2 gene (PSEN2): Mutations in the PSEN2 gene, located on chromosome 1, are also associated with early-onset familial Alzheimer's disease. Like PSEN1, this gene is involved in APP processing and beta amyloid production.

4. Apolipoprotein E (APOE) gene: Located on chromosome 19, there are three common variants of the APOE gene: APOE ε2, APOE ε3, and APOE ε4. The APOE ε4 allele is the best-known genetic risk factor for late-onset Alzheimer's disease. Having one copy of the APOE ε4 allele increases the risk, and having two children increases the risk even more.

It is important to note that the presence of any of these genetic risk factors does not guarantee the development of Alzheimer's disease. Although they increase susceptibility to disease, they are not the only determining factor. Environmental factors such as lifestyle choices, education and general health also play a role in the onset and progression of the disease.

PATHOLOGY

This is thought to be due to excessive AD production and reduced clearance of α-amyloid, with downstream events being tau hyperphosphorylation and neurotoxicity. The major pathological features of AD are brain atrophy due to focal neuronal and synaptic loss, extracellular amyloid deposition in the form of neurogenic plaques, and intraneural tau protein deposition in the form of neuronal neurofibrillary tangles. Amyloid also accumulates in blood vessels in the brain. Cerebral amyloid angiopathy is characterized by small amounts of amyloid, large deposits that disrupt arterial structures and cause cortical microinfarcts, microaneurysms, and cerebral micro- or micro-hemorrhages (many micro-hemorrhages in the occipital region of AD patients Severity ranges from Amyloid deposition is thought to begin 20 years before the onset of clinical symptoms. Longitudinal studies of amyloid-positive individuals with normal cognitive function are underway to assess the risk of future dementia in these individuals. Neurofibrillary tangles are not limited to Alzheimer's disease and occur in other conditions such as boxer's dementia, chronic traumatic encephalopathy, prion disease, and normal aging. Neurofibrillary tangle burden and neuronal loss show strong associations with overall cognitive impairment. [35,36]

NEUROLOGICAL EXAMINATION [37]

In addition to the mental status examination, neurological examination results are usually normal in people with Alzheimer's disease. Symptoms of Parkinson's disease may appear later, but these symptoms should be considered when the disease is in the early stages (for example, dementia with Lewy bodies). In the late stages of the disease, pathological reflexes such as grasping, rooting, and sucking may occur. Patients become disabled in the moderate to severe stages and eventually become mute, incontinent, and bedridden. During this period, hazardous swallowing results in many complications such as risk of aspiration, malnutrition, immobility with risk of pressure ulcers, deep vein thrombosis and infection. Often these complications are the direct cause of death in AD patients.

PHARMACOLOGICAL APPROACHES

Pharmacological approaches specific to AD are limited to three cholinesterase inhibitors (donepezil, rivastigmine and galantamine) and the NMDA receptor antagonist memantine. Cholinesterase inhibitors are approved in the United States and Europe for mild to moderate dementia due to Alzheimer's disease and not for patients with MCI. Donepezil is only approved for severe dementia in the United States. In clinical trials, these drugs have consistently shown some benefit in slowing the progression of symptoms for 6 months or slightly longer. [38/39] Side effects of cholinesterase inhibitors include nausea, vomiting, loose stools or a small number of loss of appetite, and rarely muscle twitching, headache, and bad dreams. Memantine is only approved in the United States for moderate to severe dementia due to Alzheimer's disease. The effect is also very simple.[38] Memantine has few side effects. Neither cholinesterase inhibitors nor memantine have significant effects on the basic biology of AD. Clinical trials of anti-Aβ agents with other mechanisms up to 2020 have shown no benefit.[40] One drug, aducanumab, a monoclonal antibody targeting Aβ protofibrils, is under consideration by the FDA and EMA for AD based on the results of two phase 3 clinical trials.[41] Claims of aducanumab's effectiveness are based on slowing the decline in clinical dementia rating scales, but are complicated by the fact that the study was stopped prematurely due to inconclusive results. However, an analysis of additional data found evidence to support the efficacy claims. In a phase 2 trial targeting Aβ plaque, donanemab[42] reported reductions in total Aβ and reduced rates of cognitive and functional decline. A large-scale phase 3 clinical trial is ongoing. Another monoclonal antibody, lecanemab[43], which targets oligomeric Aβ protofibrils, is in advanced research. Different treatments are available at different stages.

Clinical markers of development, such as drugs targeting tau accumulation or distribution in late development.[44] Secondary prevention trials for AD are ongoing, both involving passive immunization with Aβ. Both the API study [45] and the A4 study [46] will not report results until at least 2022. Behavioral control in people with dementia due to Alzheimer's disease is difficult to manage, especially in the moderate to severe

stages. Delusions that lead to frightening hallucinations, socially destructive behavior, or physically aggressive behavior always require pharmacological intervention. Pimavanserin, a selective inverse serotonin agonist, is currently approved in the United States and Europe for the treatment of dementia and psychosis due to Parkinson's disease.[47]

However, it is being studied in the US for broader indications, usually including dementia-related psychoses. Pimavanserin may be the only drug that has specific indications for the treatment of behavior commonly referred to as agitation, especially frightening hallucinations and delusions, physically aggressive behavior, and other socially disruptive behaviors. Atypical antipsychotics, such as quetiapine, are generally the main treatment for agitation in patients with dementia. However, this class of drugs is associated with an increased risk of death from all causes. Other antipsychotic drugs, which may be less sedating, carry the risk of developing extrapyramidal symptoms. Drug-induced parkinsonism in people with dementia is a side effect of efforts to control wakefulness.

SYMPTOM'S

Alzheimer's disease is a progressive brain disease that affects memory, thinking and behavior. Alzheimer's symptoms can vary from person to person and can get worse over time. Some common symptoms associated with Alzheimer's include:

1. Memory loss: One of the hallmarks of Alzheimer's disease is difficulty remembering new information. People may have trouble remembering recently learned information, dates, or events. Long-term memory can also be affected over time.

2. Decreased cognitive function: People with Alzheimer's disease may have difficulty thinking and reasoning. They may have trouble concentrating, solving problems, or making decisions. Complex tasks that were once routine can become increasingly difficult.

3. Language problems: People with Alzheimer's disease may have difficulty finding the right words or communicating. You may have difficulty expressing or understanding written or spoken language.

4. Disorientation and confusion: People with Alzheimer's disease often feel disoriented, especially around unfamiliar environments or times and places. They may forget where they are, how they got there, or the time and date.

5. Changes in mood and behavior: Alzheimer's disease can cause mood changes, irritability, anxiety, or depression. People may withdraw, lose interest in activities they used to enjoy, or exhibit unusual behavior changes.

6. Reduced self-care and daily tasks: Alzheimer's disease can affect people's ability to perform daily tasks, such as dressing, bathing, or grooming. They may have difficulty managing personal finances, cooking, or household chores.

7. Impaired judgment: People with Alzheimer's disease may have poor judgment or make decisions that are abnormal or out of context. It could be an issue related to money, personal hygiene, or safety.

8. Social withdrawal: As the disease progresses, people with Alzheimer's disease may withdraw from social activities and have difficulty starting a conversation or interacting with others.

They can become increasingly isolated. It is important to note that memory loss or intermittent confusion does not necessarily indicate Alzheimer's disease. However, if you or someone you know has persistent or worsening symptoms, we recommend that you get a medical evaluation and consult a healthcare professional.

MEDICATION FOR BEHAVIORAL SYMPTOMS

The first line of treatment for behavioral symptoms of AD is non-pharmacological methods. A quiet, familiar environment with door stickers and adequate lighting in all rooms is important to reduce disorientation. Aggressive behavior should always be addressed in positive and understandable language to reassure and distract the patient. Because depressive symptoms are less sensitive to anticholinergic effects, they are treated with selective serotonin reuptake inhibitors (SSRIs).[48] SSRIs can also relieve anxiety, irritability, or other nonspecific symptoms that can accompany depression. The SSRI citalopram may be helpful for agitation. Agitation or chaotic behavior may require antipsychotics for optimal treatment response. Newer "atypical" antipsychotics (quetiapine, risperidone, olanzapine) are often used in low doses with careful titration. However, both formal and atypical antipsychotics are associated with increased cardiovascular morbidity and mortality (higher for generic antipsychotics than atypical antipsychotics) and cerebrovascular side effects in older adults with dementia-related psychosis, thus raising a bleak warning. side effects: anticholinergic side effects and orthostatic and metabolic disturbances. Traditional antipsychotics are more likely to cause extrapyramidal symptoms that can affect cognitive function. All typical and atypical antipsychotics are associated with an increased risk of death when used in older people with dementia. This risk is very similar between typical antipsychotics and typical antipsychotics. This is a “black box” warning for all antipsychotics used in older adults with dementia. [49,50] Therefore, rational use of antipsychotics is indicated by frequent reassessment of treatment needs.

TREATMENT STRATEGIES FOR ALZHEIMER’S DISEASE [51]

Currently, there are four FDA-approved drugs for the management of cognitive impairment and functional impairment of general activity in symptomatic Alzheimer's disease. These include the three cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and memantine, a noncompetitive NMDA receptor modulator. Despite the tremendous efforts of the pharmaceutical industry, there are still no effective disease-modifying treatments available today. More than 20 compounds have completed phase 3 double-blind, randomized controlled trials in cohorts of patients at various stages of Alzheimer's disease, and none have shown efficacy in slowing cognitive decline or improving overall function. These many failed trials highlight the need for a diverse approach to clinical trial design in AD. First, most of the failed phase 3 trials focused on AD patients with mild to moderate symptoms. This represents an intermediate stage of the clinical disease, but an advanced stage of the biological disease, given that this pathology accumulates in the AD brain 15–20 years before the onset of clinical symptoms (Vermunt et al., 2019). At this stage of disease pathogenesis, significant and irreversible synaptic and neuronal loss has occurred, and reversing the pathological cascade can be very difficult (Gómez-Isla et al., 1996). In contrast, diseases used during preventive research tests to prevent clinical interference to prevent the disease can be opened and there can be a good opportunity to change the disease before Franc-Ano Dist. Various extensive clinical studies were the paradigm. The Board of Patients with Biomarkers (Sperling and Scrolical AD) and Arad and Apo-Senior Associative Senior, 2011). Importantly, each study tested anti amyloid therapy in patients with normal cognitive function who were at high risk of disease progression. Second, it is important to reconsider basic assumptions and assumptions about the pathogenesis of the disease. Although the evidence underlying the amyloid cascade hypothesis remains strong, new findings should continue to inform and update our understanding of disease pathobiology, ultimately leading to the development of new therapeutic approaches. The current clinical pipeline for AD includes more than 100 different compounds that are currently being tested in various stages of clinical trials (Hara et al., 2019). We review developments to identify currently available symptomatic treatment and disease-modifying therapies.

DIAGNOSTIC CRITERIA

The current diagnostic criteria for dementia are the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[53] The DSM-5 recognizes two cognitive syndromes: severe neurocognitive disorder and mild neurocognitive disorder. Sufficiently severe objective cognitive decline is required for the diagnosis of severe neurocognitive disorder. It interferes with activities of daily living and is not caused by delirium or another neurological, medical, or psychiatric condition. Patients with mild neurocognitive impairment have mild cognitive decline that does not yet deprive them of the ability to lead an independent lifestyle and perform complex daily activities such as managing finances or driving. It is important to note that DSM-5 introduces

major changes to the diagnostic criteria for cognitive impairment. The criteria no longer require the presence of memory impairment to diagnose neurodegenerative dementia as in all previous editions of the DSM. For some adult disorders, such as DSM-5, for example, roots and dementia before, memory disorders recognize that symptoms may not have early symptoms and can never be shown. Another series of promotional standards.[54]

(In other words, in the stage of the former clinic, prostate and open dementia, we have recently developed Natal entity (NAA), Alzheimer (AA) and Alzheimer (AA) Association. cognitive area or a single cognitive action and an action of the day. The NIA-AA criteria for the likelihood of Alzheimer's dementia as a dementia subtype recognized for the first time the diagnostic utility of disease biomarkers with demonstrated sensitivity, specificity, and pathologic validity. Currently, two types of biomarkers meet these criteria. Two neurodegenerative biomarkers are well known, temporal lobe atrophy on structural imaging and posterior cingulate on fluorodeoxyglucose positron emission tomography (FDGPET).[55,56] However, both are seen only in Alzheimer's dementia.

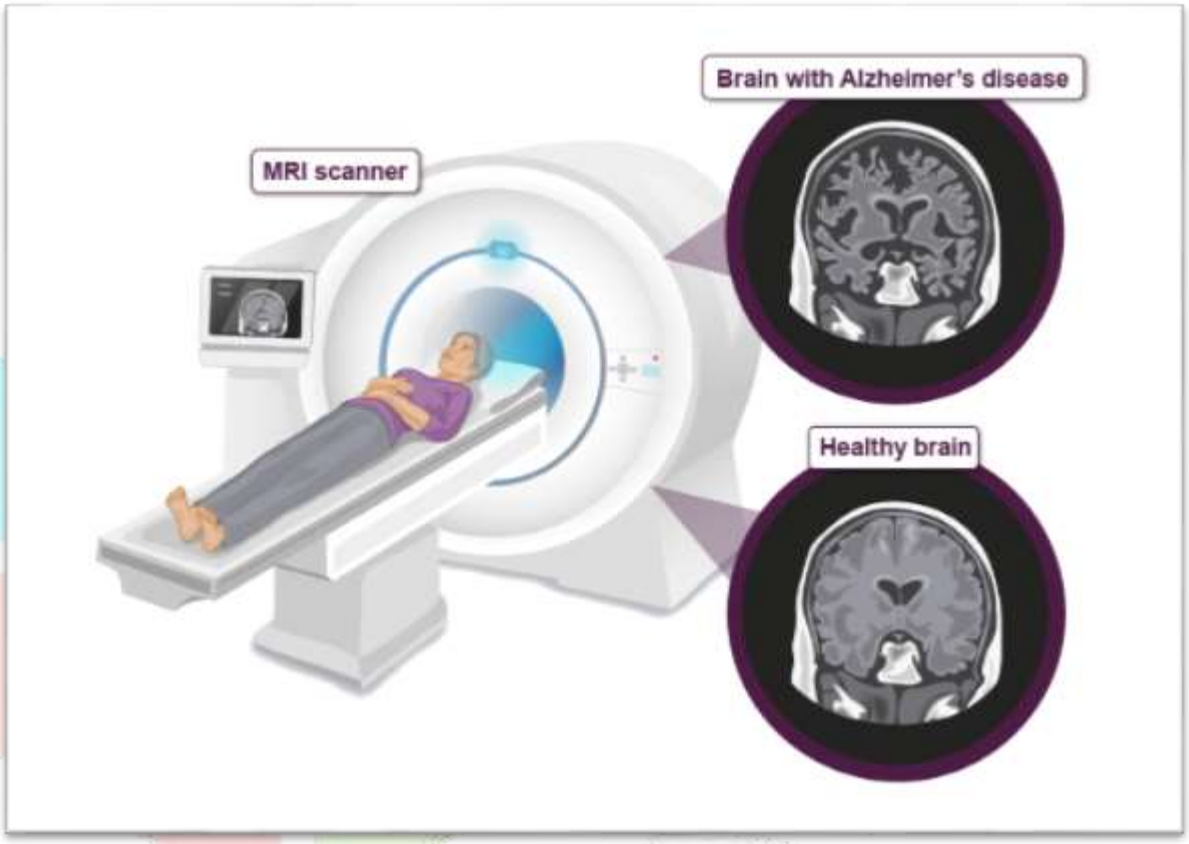

Figure 3: Diagnosis Criteria of Alzheimer's Disease

PREVENTION

Although there are no proven pharmacologic or nonpharmacologic approaches to prevent Alzheimer's disease-induced cognitive impairment, [57,60] there are reasons for optimism about multidimensional interventions that combine exercise, lifestyle modification, and cognitive stimulation.[61] Focusing on other influencing behaviors or situations may delay the onset of overt cognitive impairment. Implementation of lifestyle and medical strategies, at least in middle age, may reduce the burden of brain damage associated with cerebrovascular disease.[62] An aggressive blood pressure-lowering trial in people over 50 (including 28% of 75-year-olds) reduced MCI and dementia, although they were thought not to be cognitively impaired and safety was compromised. Systolic blood pressure in the elderly is 120 mmHg. Objectives for achieving level are discussed.[63] Reducing the overall burden of brain disease of all etiologies in cognitively significant brain regions increases the amount of AD-related pathology required to produce symptoms and delays symptomatic AD-related disease through this indirect mechanism.

RISK FACTORS

Age is the most important risk factor for dementia and Alzheimer's disease. For example, in an aging world population, such as women over 65 years of age, dementia occurs more often in women than in men because all-cause mortality is higher in men over 45 years of age.[64] Also, the prevalence of mild cognitive impairment may be higher in men.

(95% CI 1.2–2.0) for MCI in European American men and women.[65] However, in most studies, the prevalence of dementia is higher in women or there is no gender difference.[66] Genetic risk factors for AD include rare, dominantly inherited mutations in APP, PSEN1, and PSEN2, and more common but uncommon genetic variants such as APOE. Taken together, the genetic contribution accounts for only a small fraction of the observed risk at age of onset.[67] Alzheimer's disease, which is predominantly inherited, has an onset approximately 40 years earlier than late-onset sporadic Alzheimer's disease, but otherwise shares many clinical, biomarker, and pathologic similarities. Mutations in APP (encoding amyloid precursor protein (APP)), PSEN1 (encoding presenilin 1), and PSEN2 (encoding presenilin 2) cause almost all dominantly inherited Ads.[68] People with mutations in this gene are almost always younger than 65 when symptoms appear and represent a small percentage of people with AD dementia.

Alzheimer's disease and frontotemporal lobe degeneration are roughly the same age groups. A rare APP variant (A673T) has been identified to protect against Aβ production and clinical symptoms [69] More than 600 genes have been studied as susceptibility factors for AD. APOE is a susceptibility polymorphism and is a major genetic risk factor for AD. 65 years later. Carrying the APOE ε4 allele increases the risk of dementia by a factor of 3 to 4 in heterozygotes and 12 to 15 in homozygotes compared with APOE ε3 carriers.[70] Certain susceptibility genes, such as TREM2, SORL1, and ABCA7,[71] when combined, may be useful for the polygenic risk score and also explain the existence of the APOE ε4 genotype predictive of sporadic dementia due to AD.[72] Rare genetic variants are associated with a lower risk of AD than the APOE ε4 allele. Indeed, the rare R47H variant of TREM2 carries one in ten APOE ε4 heterozygotes and all other identified risk genes. 100 times stronger than APOE ε4.[73] Although variants in tau-binding proteins such as BIN1, CD2AP, FERMT2, CASS4, and PTK2B are risk genes in a wide range of analyses, mutations in MAPT (encoding tau) are not associated with AD. [74] The genetics of rare variants has played and continues to play an important role in proposing important mechanisms of Alzheimer's disease. Several potentially modifiable risk factors present in midlife, particularly metabolic factors (diabetes, hypertension, obesity, and low HDL cholesterol), hearing loss, traumatic brain injury, and alcohol abuse are associated with an increased risk of dementia later in life. life. The risks are 1.5 and 1.8.[75] Smoking, depression, low physical activity, social isolation, diabetes, and air pollution later in life are similar risk factors for dementia, but some of these, such as low physical activity, social isolation, and depression, may have bidirectional effects. Can be directional links and parts.Prodromal stage of dementia.[76] Diabetes and high blood pressure may develop.

It is the most common and most important risk factor for dementia later in life, especially when these risk factors are present in middle age as well as in later life. [77,78] Although there is some evidence for an effect of vascular risk factors in midlife on brain Aβ in later life,[79] both diabetes and hypertension are believed to cause cerebrovascular disease and, through modulatory effects, influence clinical presentation. of AD pathology. Atherosclerosis and atherosclerosis.[80]

CONCLUSION

Alzheimer's disease is a progressive neurodegenerative disease that primarily affects memory, thinking, and behavior and is the most common cause of dementia. The pathology of Alzheimer's disease involves the accumulation of abnormal proteins, including beta-amyloid plaques and tau aggregates, resulting in the loss of brain cells and disruption of neuronal connections. Early diagnosis and intervention are essential for the treatment of Alzheimer's disease. Current diagnostic methods include comprehensive assessments, cognitive tests, and neuroimaging techniques. There is no cure for Alzheimer's disease, but available treatments aim to manage symptoms, improve quality of life, and slow the progression of the disease. Medications such as cholinesterase inhibitors and memantine are often prescribed. non-pharmacological interventions, including cognitive stimulation, exercise, social activity, and a healthy lifestyle, can have beneficial effects in managing Alzheimer's symptoms and supporting overall brain health. 6. Current research aims to deepen our understanding of the mechanisms of Alzheimer's disease, develop more accurate diagnostic tools and explore new treatment strategies. This includes investigating possible drug treatments, immunotherapy, and lifestyle interventions.

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