ALZHEIMER’S DISEASE

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ABSTRACT

Alzheimer's disease is a progressive disorder that causes brain cells to degenerate and die. It is the most common cause of dementia—a continuous decline in thinking, behavioural and social skills that disrupts a person's ability to function independently. The early signs of the disease may be forgetting recent events or conversations. As the disease progresses, a person with Alzheimer's disease will develop severe memory impairment and lose the ability to carry out everyday tasks. Current Alzheimer's disease medications may temporarily improve symptoms or slow the rate of decline. These treatments can sometimes help people with Alzheimer's disease maximize function and maintain independence for a time. Different programs and services can help support people with Alzheimer's disease and their caregivers. In advanced stages of the disease, complications from severe loss of brain function — such as dehydration, malnutrition or infection — result in death. Cholinesterase inhibitors that are approved for symptomatic relief in the U.S.A include Donepezil (Aricept), Rivastigmine (Exelon) and Tacrine (Cognex).

KEYWORDS: Dementia, Amyloid Proteins, Tau Proteins, Plaques.
INTRODUCTION

Alzheimer’s disease is a progressive form of dementia. Dementia is a broader term for conditions caused by brain injuries or diseases that negatively affect memory, thinking, and behaviour. These changes interfere with daily living. According to the Alzheimer’s Association, Alzheimer’s disease accounts for 60 to 80% of dementia cases. Most people with the disease get a diagnosis after age 65. If it's diagnosed before then, it's generally referred to as early onset Alzheimer’s disease. There’s no cure for Alzheimer’s, but there are treatments that can slow the progression of the disease. ¹

Alzheimer’s facts

Although many people have heard of Alzheimer’s disease, some aren’t sure exactly what it is. Here are some facts about this condition:

- Alzheimer’s disease is a chronic on-going condition.
- Its symptoms come on gradually and the effects on the brain are degenerative, meaning they cause slow decline.
- There’s no cure for Alzheimer’s but treatment can help slow the progression of the disease and may improve quality of life.
- Anyone can get Alzheimer’s disease but certain people are at higher risk for it. This includes people over age 65 and those with a family history of the condition.
- Alzheimer’s and dementia isn’t the same thing. Alzheimer’s disease is a type of dementia.
- There’s no single expected outcome for people with Alzheimer’s. Some people live a long time with mild cognitive damage, while others experience a more rapid onset of symptoms and quicker disease progression.

Dementia vs Alzheimer’s disease

The terms “dementia” and “Alzheimer’s” are sometimes used interchangeably. However, these two conditions aren’t the same. Alzheimer’s is a type of dementia. Dementia is a broader term for conditions with symptoms relating to memory loss such as forgetfulness and confusion. Dementia includes more specific conditions, such as Alzheimer’s disease, Parkinson’s disease, traumatic brain injury, and others, which can cause these symptoms. Causes, symptoms, and treatments can be different for these diseases. [1]

Alzheimer’s disease (AD) is the most frequent cause of dementia [2]. In most cases, the progression of the disease is slow with disease duration of approximately 10 years while rapid progression is observed in some cases [3-5]. Rapid progression can be defined by decline on psycho-
metric tests such as the Mini Mental State Examination score, e.g. 5 points/year [4], or on a basis of survival time, e.g. less than 4 years [6].

Alzheimer’s disease (AD) pathology is characterized by abnormal aggregation of the proteins amyloid- (A) and hyper phosphorylated tau accompanied by brain inflammation in the form of microglial activation [7, 8]. No effective disease-modifying therapies are currently available for AD. To date, immunotherapy trials, with both passive anti amyloid and anti tau antibodies and vaccines, while proving effective in lowering the abnormally aggregated protein load, have generally proved ineffective in improving cognitive status with one possible exception (aducanumab) though further trials are currently running in mild cognitive impairment and amyloid positive elderly subjects without cognitive symptoms [9, 10].

Considerable evidence suggests that the pathogenetic process of Alzheimer’s disease includes a long latent (asymptomatic) stage before mild cognitive problems appear as a prodrome of dementia. Although later interventions may retard symptomatic progression, the latent stage appears to be the ideal time for application of a prevention strategy. Several candidate agents for this strategy have been identified. These include postmenopausal oestrogen replacement, consumption of red wine, use of histamine H2 blockers and use of aspirin. [9, 10].

SYMPTOMS

I. The First Stage: Mild Alzheimer’s Dementia

A person experiencing the earliest symptoms of Alzheimer’s disease may still be able to work, drive, take part in social activities, and otherwise live independently. But they may begin to experience problems with memory or concentration. They may have trouble retaining new information — remembering the name of someone they’ve just met, for instance, or recalling material they’ve just read. Unfortunately, this symptom is often dismissed as a normal part of ageing or the result of stress, delaying diagnosis and treatment. [11]

Other common symptoms of mild Alzheimer’s include:

- Misplacing items
- Language problems, such as having trouble coming up with the right words
- Trouble planning, organizing, or solving problems
- Losing a sense of time
- Vision-related problems, such as with depth perception and color contrast
- Increasingly poor judgment leading to bad decisions
- Mood and personality changes, such as becoming confused, anxious, irritable, or depressed
- Difficulty completing familiar home, work, or leisure tasks, such as managing a budget
- Withdrawal from work or social engagements.
II. The Second Stage: Moderate Alzheimer’s Dementia

In most cases of moderate Alzheimer’s dementia, the disease has spread to areas of the brain that control language, reasoning, sensory processing, and conscious thought, causing previous symptoms to become more pronounced. Damage to the brain can make it difficult for people to say what they’re thinking or complete basic tasks, such as paying bills. But they may still remember important details about their personal history. This is typically the longest stage, potentially lasting for many years. [11]

Symptoms of this period may include

- Increased memory loss and confusion, including forgetting names or personally significant events
- Trouble recognizing family and friends
- Inability to learn new things or cope with new situations
- Hallucinations, delusions, and paranoia
- Loss of impulse control, such as undressing at inappropriate times or using vulgar language
- Repetitive statements or movements, such as hand-wringing or tissue-shredding
- Trouble carrying out activities that require multiple steps, such as getting dressed
- Difficulty reading, writing, or working with numbers
- Incontinence
- Behavioral problems, such as moodiness or inappropriate anger outbursts
- Restlessness, agitation, anxiety, tearfulness, and increased risk of wandering, especially in the late afternoon or evening (a condition called sun downing)

III. The Third Stage: Severe Alzheimer’s Dementia

People with severe Alzheimer’s dementia are completely dependent on others for around-the-clock care. They become increasingly unable to respond to their environment, communicate, and perform basic daily activities, such as dressing, eating, or bathing. They become bedridden or chair-bound. Eventually, they become unable to control movement. This stage may last from several weeks to several years. [11]

Other symptoms of advanced Alzheimer’s may include

- Seizures
- Weight loss
- Increased risk of infections, including skin infections and pneumonia
- Failure to recognize family and friends
- Increased sleeping
- Groaning, grunting, and moaning
- Difficulty swallowing
- Loss of bowel and bladder control

Researchers have not found a specific gene that directly causes the late-onset form of the disease. However, one genetic risk factor—having one form of the Apolipoprotein E (APOE) gene
on chromosome 19—does increase a person's risk. APOE comes in several different forms, or alleles.

- APOE ε2 is relatively rare and may provide some protection against the disease. If Alzheimer's disease occurs in a person with this allele, it usually develops later in life than it would in someone with the APOE ε4 gene.
- APOE ε3, the most common allele, is believed to play a neutral role in the disease—neither decreasing nor increasing risk.
- APOE ε4 increases risk for Alzheimer's disease and is also associated with an earlier age of disease onset. A person has zero, one, or two APOE ε4 alleles. Having more APOE ε4 alleles increases the risk of developing Alzheimer's. APOE ε4 is called a risk-factor gene because it increases a person's risk of developing the disease. However, inheriting an APOE ε4 allele does not mean that a person will definitely develop Alzheimer's. Some people with an APOE ε4 allele never get the disease, and others who develop Alzheimer's do not have any APOE ε4 alleles. [11]

**EARLY-ONSET ALZHEIMER'S DISEASE**

Early-onset Alzheimer's disease occurs between a person's 30s to mid-60s and represents less than 10 percent of all people with Alzheimer's. Some cases are caused by an inherited change in one of three genes, resulting in a type known as early-onset familial Alzheimer's disease, or FAD. For other cases of early-onset Alzheimer's, research suggests there may be a genetic component related to factors other than these three genes. A child whose biological mother or father carries a genetic mutation for early-onset FAD has a 50/50 chance of inheriting that mutation. If the mutation is in fact inherited, the child has a very strong probability of developing early-onset FAD. Early-onset FAD is caused by any one of a number of different single gene mutations on chromosomes 21, 14, and 1. Each of these mutations causes abnormal proteins to be formed. Mutations on chromosome 21 cause the formation of abnormal amyloid precursor protein (APP). A mutation on chromosome 14 causes abnormal presenilin 1 to be made, and a mutation on chromosome 1 leads to abnormal presenilin 2. Each of these mutations plays a role in the breakdown of APP, a protein whose precise function is not yet fully understood. This breakdown is part of a process that generates harmful forms of amyloid plaques, a hallmark of Alzheimer's disease. [11]

**ETIOLOGY**

Like all types of dementia, Alzheimer's is caused by brain cell death. It is a neurodegenerative disease, which means there is progressive brain cell death that happens over time. In a person with Alzheimer's, the tissue has fewer and fewer nerve cells and connections. Autopsies have shown that the nerve tissue in the brain of a person with Alzheimer's has tiny deposits, known as plaques and tangles, that build up on the tissue. The plaques are found between the dying brain cells, and they are made from a protein known as beta-amyloid. The tangles occur within the nerve cells, and they are made from another protein, called tau. Researchers do not fully understand why these changes occur. Several different factors are believed to be involved. [11].
Risk factors

Unavoidable risk factors for developing the condition include:

- Ageing
- A family history of Alzheimer's
- Carrying certain genes

Factors that increase the risk include:

- Undergoing severe or repeated traumatic brain injuries (TBI)
- Exposure to some environmental contaminants, such as toxic metals, pesticide, and industrial chemicals.

To reduce the risk of TBI-related dementia, it is important always to wear a safety belt when traveling by car, to take precautions when playing contact sports, and to following health instructions and guidelines to ensure sufficient rest and recovery if an injury does occur. A moderate TBI appears to double the risk of having dementia, while a severe TBI increases it 4.5 times. [12]

Late-Onset Alzheimer's disease:

Most people with Alzheimer's have the late-onset form of the disease, in which symptoms become apparent in the mid-60s. Researchers have not found a specific gene that directly causes the late-onset form of the disease. However, one genetic risk factor—having one form of the apolipoprotein E (APOE) gene on chromosome 19—does increase a person's risk. APOE comes in several different forms, or alleles. [11]

DIAGNOSIS

There is no single test for Alzheimer's disease, so doctors will look at the signs and symptoms, take a medical history, and rule out other conditions before making a diagnosis. They may also check the person's neurological function, for example, by testing their balance, senses, and reflexes. Other assessments may include a blood or urine test, a CT or MRI scan of the brain, and screening for depression. Sometimes the symptoms of dementia are related to an inherited disorder such as Huntington's disease, so genetic testing may be done. After ruling out other possible conditions, the doctor will carry out cognitive and memory tests, to assess the person's ability to think and remember. [12]

Cognitive assessment

To confirm a diagnosis of Alzheimer's, the following must be present and severe enough to affect daily activities:

- Gradual memory loss
- Progressive cognitive impairment
Questions that may be asked to test cognitive ability include:

- What is your age?
- What is the time, to the nearest hour?
- What is the year?
- What is the name of the hospital or town we are in?
- Can you recognize two people, for example, the doctor, nurse, or caregiver?
- What is your date of birth?
- In which year did (a well-known historical event) happen?
- Name the president.
- Count backward from 20 down to 1
- Repeat an address at the end of the test that I will give you now (for example, "42 West Street"). A number of assessment tools are available to assess cognitive function.

Genetic testing

In some cases, genetic testing may be appropriate. A gene known as the APOE-e4 is associated with higher chances of people over the age of 55 years developing Alzheimer's. Using this test early could indicate the likelihood of someone having or developing the disease. However, the test is controversial, and the results are not entirely reliable. In the future, emerging biological tests may make it possible to assess for biomarkers in people who may be at risk of Alzheimer's.

Neuropsychological tests

You may be evaluated by a specialist trained in brain conditions and mental health conditions (neuropsychologist). The evaluation can include extensive tests to evaluate your memory and thinking (cognitive) skills. These tests help doctors determine if you have dementia, and if you're able to safely conduct daily tasks such as driving and managing your finances. They provide as much information on what you can still do as well as what you may have lost. These tests can also evaluate if depression may be causing your symptoms.

Interviews with friends and family

Doctors may ask your family member or friend questions about you and your behavior. Doctors look for details that don't fit with your former level of function. Your family member or friend often can explain how your thinking (cognitive) skills, functional abilities and behaviors have changed over time. This series of clinical assessments, the physical exam and the setting (age and duration of progressive symptoms) often provide doctors with enough information to make a diagnosis of Alzheimer's dementia. However, when the diagnosis isn't clear, doctors may need to order additional tests. [13]

Laboratory tests

You may have laboratory tests to rule out other disorders that cause some symptoms similar to those of Alzheimer's dementia, such as a thyroid disorder or vitamin B-12 deficiency.
Brain-imaging tests

Alzheimer's dementia results from the progressive loss (degeneration) of brain cells. This degeneration may show up in a variety of ways in brain scans. However, these scans alone aren't enough to make a diagnosis. Scans aren't used to diagnose the condition because there is overlap in what doctors consider normal age-related change in the brain and abnormal change. [13]

However, brain imaging can help

- Rule out other causes, such as hemorrhages, brain tumors or strokes
- Distinguish between different types of degenerative brain disease
- Establish a baseline about the degree of degeneration.
- The brain-imaging technologies most often used are:
  - Magnetic resonance imaging (MRI): An MRI uses powerful radio waves and magnets to create a detailed view of your brain.
  - Computerized Tomography (CT): A CT scan uses X-rays to obtain cross-sectional images of your brain.
  - Positron emission tomography (PET): A PET scan uses a radioactive substance known as a tracer to detect substances in the body. There are different types of PET scans. The most commonly used PET scan is a fluorodeoxyglucose (FDG) PET scan, which can identify brain regions with decreased glucose metabolism. The pattern of metabolism change can distinguish between different types of degenerative brain disease. PET scans have recently been developed that detect clusters of amyloid proteins (plaques), which are associated with Alzheimer's dementia, but this type of PET scan is typically used in the research setting. [13]
  - To the patients with Alzheimer's dementia, doctors can offer drug and non-drug interventions that may ease the burden of the disease. Doctors often prescribe drugs that may slow the decline in memory and other cognitive skills. You may also be able to participate in clinical trials. [13] Also, doctors can teach you and your caregivers about strategies to enhance your living environment, establish routines, plan activities and manage changes in skills to minimize the effect of the disease on your everyday life. Importantly, an early diagnosis also helps you, your family and caregivers plan for the future.
    You'll have the chance to make informed decisions on a number of issues, such as:
    - Appropriate community services and resources
    - Options for residential and at-home care
    - Plans for handling financial issues
    - Expectations for future care and medical decisions

TREATMENT

There is no known cure for Alzheimer's. The death of brain cells cannot be reversed. However, there are therapeutic interventions that can make easier for people to live with the disease.
According to the Alzheimer's Association, the following are important elements of dementia care:

- Effective management of any conditions occurring alongside the Alzheimer's
- Activities and day-care programs
- Involvement of support groups and services

How to Choose a Treatment

Your doctor will help you choose the best treatment based on a few things about you, including:

- Your age, overall health, and medical history
- How severe your disease is
- How well a medicine or therapy will work for you and your lifestyle
- Your preferences or those of your family or care giver

Drug therapy

No disease-modifying drugs are available for Alzheimer's disease, but some options may reduce the symptoms and help improve quality of life. Cholinesterase inhibitors that are approved for symptomatic relief in the U.S.A include:

- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Tacrine (Cognex) A different kind of drug, memantine (Namenda), an NMDA receptor antagonist, may also be used, alone or in combination with a cholinesterase inhibitor.

Other therapy

The need for quality-of-life care becomes more important as the person becomes less able to live independently.

Other Medications which can Help

Some drugs curb the breakdown of a chemical in the brain, called acetylcholine, that’s important for memory and learning. They may slow down how fast symptoms get worse for about half of people who take them. The effect lasts for a limited time, on average 6 to 12 months. Common side effects are usually mild for these medications and include diarrhea, vomiting, nausea, fatigue, insomnia, loss of appetite, and weight loss. There are three drugs of this type: donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon).

Goals

The goals of the present review are those listed below in order to re-evaluate the efficacy of memory rehabilitation for patients with mild to moderate AD:
To provide a succinct historical review of the traditional techniques adopted in the rehabilitation of memory in AD, focusing on the theoretical considerations that provided the foundation for the current scepticism towards this type of therapeutic intervention.

To discuss the recent memory rehabilitation procedures that have proven clinically effective or relevant to practical, everyday needs of mild to moderate AD patients, augmented by the authors' ongoing intervention research. [11]

Modifiable factors that may help prevent Alzheimer's include:

- Getting regular exercise
- Maintaining a healthy cardiovascular system
- Managing the risk of cardiovascular disease, diabetes, obesity, smoking, and high blood pressure
- Following a varied and healthful diet
- Participating in lifelong learning and cognitive training

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