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Alzheimer Disease

K. R. Reddy

ABSTRACT

A review about Alzheimer disease. Stages of Alzheimer's disease and researches carried out for determination of Alzheimer disease before the actual symptoms of disease occur, genetic predisposition, and treatment of Alzheimer disease.

KeyWords

Alzheimer disease, neurofibrillary tangles, and amyloid plaques, memory loss, and cognitive impairment.

Abbreviations

AD, Alzheimer disease, FAD, familial Alzheimer disease, APOE, apolipoprotein, alleles, APP, amyloid precursor protein.

INTRODUCTION

- **Discovered by: Dr. Alois Alzheimer.**

Name: Dr Alois Alzheimer, Birth: June 14,1864 in Marktbreit, Germany, Education: Medicine from University of Wuburg and Berlin in 1887.

- **Works of Dr. Alois Alzheimer**

Worked as medical officer at the state asylum in Frankfurt am Main. Became famous neurologist publishing works on epilepsy, brain tumors, syphilis, and hardening of arteries. Correlated clinical course of the patient with changes observed in brain when autopsies were performed on their brain after death.

- **Discovery status**

In 1901 Dr. Alois Alzheimer met a 51-year-old woman named Auguste D. who was first patient of Dr. Alois Alzheimer when he worked in asylum and was under care of Dr. Alzheimer for 4 years until her death. The patient showed symptoms of memory loss, speech in coordination, confusion, wandering, screaming, and agitation. She showed symptoms of poor bladder control (incontinence) and was unaware of her surroundings.

After death of the patient, on autopsy Dr. Alzheimer noticed that her brain had shriveled and neurons had disappeared. He discovered neurofibrillary tangles and senile plaques which are now hallmark of Alzheimer disease.

After his presentation of findings in 1906, the disease was named after him and was known to be most common form of dementia in older people.

In 1960's the medical community concluded Alzheimer as a disease and not normal part of aging when they discovered the link between decline in cognitive ability and development of plaques and tangles in brain.

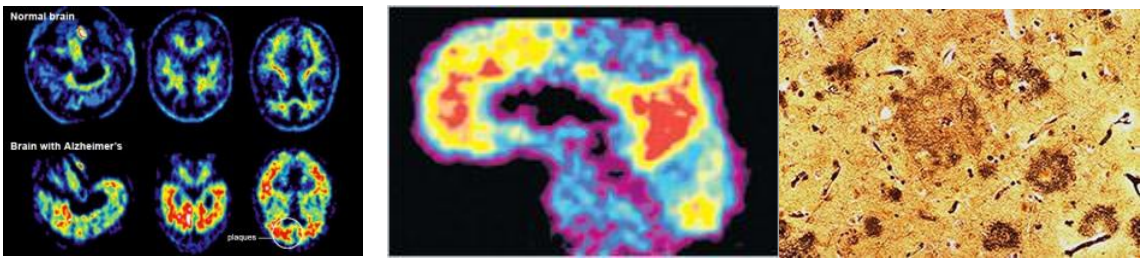

Fig: amyloid plaques MRI image of amyloid plaques in brain

SYMPTOMS

- **Memory problems:** Difficulty remembering information that is recent, forgetting more and more and inability to recall information later on.

- **Language and communication difficulties:** People with Alzheimer's will have difficulty communicating and understanding information that is being spoken about which is indicator of early sign of Alzheimer.

- **Lapses in judgement:** The decision making process is significantly affected resulting in unwise personal, social, and financial decisions.

- **Problems completing familiar tasks**: Completing a simple task which is familiar may pose a great difficulty in Alzheimer patient.

- **Disorientation:** Disorientation with time and place and confused about current time, day, date, month, season, and/or year.

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- **Decreased ability to think abstractly:** The patients have trouble completing complex intellectual tasks
- **Misplacing objects**: The most common indicator of Alzheimer's is losing something and inability to find them.
- **Changing mood or behaviour:** Mood swings are unpredictable with moods changing in fraction of seconds.
- **Shifts in personality:** Changes in personality occur. Apathy or loss of initiative. Apathy increases to a degree that it affects day-to-day functioning.

STAGES OF ALZHEIMER'S

Progressive degeneration of brain cells is characteristic feature of Alzheimer's disease.

- **Early stage**

Also known as "mild Alzheimer's disease" refers to people of any age who have mild impairment however differs from term "early onset" which is usually used in case of people who have been diagnosed with Alzheimer's disease at a younger age than usual. Common symptoms in the early stage include communication difficulties, forgetfulness, and changes in behaviour and mood. People in early stage need little help as they know how they are changing, willing to talk to others about their experience of living with the disease, and also wish to seek help to plan and direct their future care.

- **Middle stage**

Also known as "moderate Alzheimer's disease." In this stage, there is continued deterioration of thinking and memory although the person is aware of their condition. Middle stage is a point where families and caregivers may increasingly need to provide care. This may include moving the person to care facility. It is the longest stage.

- **Late stage**

ALSO KNOWN AS "SEVERE" OR "ADVANCED." PEOPLE IN THIS STAGE HAVE DECREASED MENTAL ABILITY. THEY ARE UNABLE TO VERBALLY COMMUNICATE AND TAKE CARE OF THEMSELVES. THEY BECOME FRAIL PHYSICALLY AND NEED 24-HOUR CARE. CARE AT THIS STAGE USUALLY INVOLVES PROVIDING SUPPORT TO THE PERSON AND FURTHER DECISION MAKING THROUGHOUT THE LATE STAGE.

CAUSES

- **Researches**

1. Research by Mount Sinai School of Medicine

Specimen: A mice modified to develop Alzheimer disease was used.

Indications of Alzheimer's disease may be evident decades before first signs of cognitive impairment. The researchers found that patients with Alzheimer's disease show lower glucose utilization in the brain when compared to people with normal cognitive function and this in fact is

evident approximately 20 years before the actual symptoms of Alzheimer are detected in a patient. This study was published online in the journal of *translational neuroscience.*

Findings: Beta-amyloid is an abnormal protein linked to Alzheimer disease which becomes detectable in brain in soluble toxic form. Mitochondrion of cell where glucose is converted into energy becomes impaired.

Conclusion: Therefore mice with decreased energy metabolism developed signs of Alzheimer disease. Time frame in mice when beta-amyloid is detectable is equivalent to about 20 human years before actual symptoms development. Therefore diagnosis in mice validates Alzheimer's disease may be the end result of brain cell energy production.

2. Research by Mount Sinai hospital

Specimen: A mice modified to develop Alzheimer disease was used.

Findings: A gene named proliferator-activated receptor co-activator 1 (PGC-1), a key regulator of glucose currently investigated as a potential therapeutic target for type 2 diabetes is decreased in Alzheimer's disease and this decreased may be casually linked to Alzheimer disease. PGC-1 promotes degradation of specific enzyme known as beta-secretase (BACE). ACE is involved in processing and eventually degeneration of beta-amyloid, an abnormal protein linked with brain degradation and Alzheimer.

Conclusion: To find that PGC-1 is common denominator between diabetes and Alzheimer's disease. PGC-1 can be manipulated pharmacologically to prevent BACE accumulation in the brain.

3. Researched in Pittsburgh School of Medicine in collaboration with scientist and National Institutes of Health. Published in public library of science one. led by first author Thomas Miller, Ph.D., and senior author David D. Roberts, Ph.D., both of the Laboratory of Pathology in NIH's National Cancer Institute (NCI).

Alzheimer disease leads to loss of nitric oxide in brain.

Specimen: Mouse and human cell.

Findings: Amyloid beta, the main component of plaques that accumulate on brain cells in Alzheimer binds to cell surface receptor called CD36 which causes decrease activity of soluble guanylate cyclise to reduce NO signalling but this inhibition required interaction with CD47 another cell surface protein.

Alzheimer disease interacts with certain cellular protein to inhibit normal blood flow to the brain. NO is a signalling molecule that helps regulate blood flow, immune and neurological processes is low in people who have Alzheimer disease. It is evident that NO can protect neurons from degenerating and dying.

Conclusion: An agent that blocks either CD36 or CD47 could slow neuronal degeneration in Alzheimer's by protecting production of NO in brain. Dr. Isenberg involved in research quoted "Importantly, we have already identified therapeutic agents that can interrupt the inhibitory signal induced by these interactions to maximize NO production, signalling and sensitivity."

GENETIC PREDISPOSITION

- **Late onset**

Most cases of Alzheimer's are the late-onset form, which develops after age 60. Link between Alzheimer's disease and genes on four chromosomes, labelled numerically as 1, 14, 19, and 21. The *APOE* gene on chromosome 19 has been linked to late-onset Alzheimer's disease, which is the most common form of the disease. However, APOE gene is not a consistent genetic marker of disease because many people who have *APOE4* variant do not develop Alzheimer's disease and many people develop the disease although they have no APOE4 variant

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Apolipoprotein E (APOE) gene specifically APOE allele 4 that is APOE4 is also known as risk factor gene found on chromosome 19.
APOE basically contains the instructions for making a protein that helps carry cholesterol and other types of fat in the bloodstream. APOE and its **alleles**. Three forms—APOE ε2, APOE ε3, and APOE ε4—occur most frequently.

- APOE ε2, it is relatively rare and person with this type of allele who develops Alzheimer disease usually belongs to late onset Alzheimer disease category.
- APOE ε3, the most common allele and plays a neutral role neither decreasing nor increasing the risk of Alzheimer disease.
- APOE ε4 is present in about 25 to 30 percent of the population and about 40 percent of all people with late-onset Alzheimer's. People who develop Alzheimer's are more likely to have an APOE ε4 allele than people who do not develop the disease.

Genome-wide association study (GWAS) is a new approach in which researchers have identified various genes in addition to APOE ε4 that may increase risk for late-onset Alzheimer's, including BIN1, CLU, PICALM, and CR1.

Early-onset Alzheimer's disease occurs in people aged between 30 to 60, it is rare, occurring in less than 5 percent of all people who have Alzheimer's.

Causes of early-onset Alzheimer's are usually unknown but most cases are inherited, a type known as familial Alzheimer's disease (FAD). It is caused by single-gene mutations on **chromosomes** 21, 14, and 1 causing different abnormal protein 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.

DRUG TREATMENT

No drug treatments are available to provide cure for Alzheimer disease however drug treatment is usually prescribed in order to control symptoms of Alzheimer's like drugs used to relieve depression and treat behavioural symptoms and dealing with aggressive behaviour.
There are mainly 2 types of medications used in Alzheimer's

- **Cholinesterase inhibitors and NMDA receptor antagonists.**

Cholinesterase inhibitors include donepezil hydrochloride (Aricept), rivastigmine (Exelon) and galantamine (Reminyl) prevent breaking down of acetylcholine by enzyme acetylcholinesterase by blocking it as a result of which there is increased concentration of acetylcholine in the brain leading increased communication between the nerve cells which use acetylcholine as a chemical messenger, which may temporarily improve or stabilise the symptoms of Alzheimer's disease.

- **The NMDA receptor antagonist is memantine (Ebixa).**

Memantine blocks chemical messenger glutamate which is released in excessive amounts when brain cells are damaged. Memantine blocks effects of excess glutamate which can protect brain cells.

Dose of drugs

1. Donepezil (Aricept) 5- 10 mg tablet a day at bedtime.
2. Rivastigmine (Exelon) maximum licensed dose is 12 mg capsules or oral solution taken twice a day. Patches are alternative options for people who are not comfortable with oral medication.
3. The recommended starting dose for galantamine (Reminyl) is 8mg and licensed dose is 24 mg . each a day for four weeks.
4. Memantine (Ebixa) comes in two forms, as 10mg and 20mg tablets, taken with or without food.

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