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A REVIEW ON ALZHEIMER'S DISEASE

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Abstract:

Alzheimer's disease is an irreversible, progressive brain disease that slowly destroys memory and thinking skills. The prevalence is 3% for persons 65-74 years old, 19% for those 75-84 years pld and 47% for those over 85 years old. Ad is mainly clinically manifested with dementia. The etiology of AD includes cholinergic, amyloid, tau hypothesis. Pathogenesis of AD involves the apperance of extra cellular beta-amyloid plaques and intra cellular neurofibrillary tangles. Drugs mainly includes Anticholinesterases. The recent reserchers using various animal modles are promising a definite and complete treatment for AD in coming years. Above everything it is the love and affection of the family that is what required for AD patient. Alzheimer's patients are exactly like any other patients in that they need plenty of care, support, patience, and love.AD patients show increased level of miRNAs are considered promising non-invasive candidates for AD diagnosis and prognosis.

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INTRODUCTION:

Alzheimer's disease is the most common form of dementia, a neurological disease. Alzheimer's disease usually has a gradual decline in mental functions, often beginning with that results in the loss of memory, language skills & activities of daily living.

Alzheimer's disease is a neurodegenerative disease that in its most common form is found in people over age 65 approxmiately 24 million people worldwide are living with Alzheimer's clinical signs of Alzheimer's disease are characterized by progressive cognitive deterioration.

It is the most common type of dementia. Plaques which contains misfolded proteins called beta amyloid form in the brain medications can help to reduced the symptoms of the disease but they cannot change the course of underlying pathology. Genetic factors are suspected and dominant mutations in 3 different genes have been identified that account for the small number of cases of early onset alzheimer's disease.

According to the leading disease theory called the "amyloid Hypothesis" the prime suspect is a tiny protein fragement called beta-amyloid . Trouble begins when identified factors trigger over production of beta-amyloid or reduce the brain's stability to dispose it. The over jams signaling at the synapses ,blocking information flow and leading to the "cascade" of damaging the events in cell death.

Plaques considered to be one of pathological hall mark of Alzheimer's.

The other hallmark is tangles formed when a different protein called tau twists in to strands inside dead and dying neurons. Some abnormalities seen in Alzheimer brain tissue include inflammation and oxidative stress ,damage from high reactive oxygen containing products of cellular metabolism.

CAUSES (ETIOLOGY):

Scientists believe that for most people alzheimers disease is caused by a combination of genetic, lifestyle and environmental factors that effect the brain overtime.

Less than 1% of the time ,alzheimers is caused by specific genetic changes that virtually guarantee a person will develop the disease.These rare occurrences usually resulting disease onset in middle age.

The exact causes of alzheimers disease are not fully understood , but at its core are problems with brain proteins that fail to function normally, disrupt the work of brain cells(neurons) and unless a series of toxic events. Neurons are damaged loose connections to each other and eventually die.

The damage most often starts in the region of the brain that controls memory, but the process begins years before the first symptoms. The loss of neurons spreads in a some what predictable pattern to other region of the brains. By the late stage of disease the brain has shrunk significantly.

RISK FACTORS:

*Age is the first most important known risk factor for alzheimer's disease.
*Environmental exposure to aliminium .
*It is caused in case of major head injuries.
*Smoking
*Mental stress and physical life style.Scientists are still trying to fully understand the cause or causes of Alzheimer's disease. In the meantime, it's helpful to understand the hallmarks of Alzheimer's plaques and tangles and the risk factors that affect a person's likelihood of developing the disease.

PATHOPHYSIOLOGY:

Biochemistry:

Alzheimer's disease has been identified as a protein misfolding disease, or proteopathy, due to accumulation of abnormally folded amyloid beta protein and tau protein in the brains of AD patients. Amyloid beta, also written Aβ, is a short peptide that is a proteolytic byproduct of the transmembrane protein amyloid precursor protein(APP), whose function is unclear but thought to be involved in neuronal development.Thepresenilins are omponents of proteolytic complex involved in APP processing and degradation. Although amyloid beta monomers are soluble and harmless, they undergo a dramatic conformational change at sufficiently high concentration to form a beta sheet rich tertiary structure that aggregates to form amyloid fibrils that deposit outside neurons in dense formations known as SENILE PLAQUES OR NEURITIC PLAQUES, in less dense aggregates as diffuse plaques, and sometimes in the walls of small blood vessels in the brain in a process called amyloid angiopathy or congophlic angiopathy.

Enzymes act on the APP (amyloid precursor protein) and cut it into fragments.The beta- amyloid fragment is crucial in the formation of sensile plaques in AD.

In Alzheimer's disease, changes in tau protein lead to the disintegration of microtubles in brain cells.

Alzheimer's disease is also considered a tauopathy due to abnormal aggregation of the tau protein. Every neuron has a cytoskeleton, an internal support structure partly made up of structures called microtubles.Thesemicrotubles act like tracks, guiding nutrients and molecules from the body of the cell to the ends of the axon and back.

AD is also considered a tauopathy due to abnormal aggregation of the tau protein, a microtubule-associated protein expressed in neurons that normally acts to stabilize microtubules in the cell cytoskeleton.Like most microtubule-associated proteins, tau is normally regulated by phosphorylation; however, in AD patients, hyperphosphorylated tau accumulates as paired helical filaments that iturn aggregate into masses inside nerve cell bodies known as neurofibrillary tangles and as dystrophic neurites associated with amyloid plaques.

Neuropathology

Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in brains of those afflicted by AD. Plaques are dense, mostly insouble deposits of beta amyloid peptide and cellular material outside and around neurons. Neurofibrillary tangles are aggregates of the microtubule associated protein tau which has become hyperphosphorylated and accumulate inside the cells themselves.Although many older individuals develop some plaques and tangles as a consequence of ageing, the brains of people with AD have a greater number of them in specific brain regions such as the temporal lobe.Lewy bodies are not rare in the brain of people with AD.

Plaques and Tangles

The formation of amyloid plaques and neurofibrillary tangles are thought to contribute to the degradation of the neurons (nerve cells) in the brain and the subsequent symptoms of Alzheimerdisease.

Disease mechanism

Exactly how disturbances of production and aggregation of the beta-amyloid peptide give rise to the pathology of AD is not known. The amyloid hypothesis traditionally points to the accumulation of beta-amyloid peptides as the central event triggering neuron degeneration. Accumulation of aggregated amyloid Fibrils, which are believed to be the toxic form of the protien responsible for disrupting the cell's calcium ion homeostasis, induces programmed cell death(apoptosis). It is also known that Aβ selectively builds up in the mitochondria in the cells of alzheimer's-affected brains, and it also inhibits certain enzyme functions and the utilization of glucose by neurons.

Various inflammatory processes and cytokines may also have a role in the pathology of alzheimer's disease. Inflammation is a general marker of tissusedamage in any disease, and may be either secondary to tissue damage in AD or a marker of an immunological response. There is increasing evidence of a strong interaction between the neurons and immunological mechanisms in the brain.Obesity and systemic inflammation may interfere with immunological processes which promote disease progression.

Aletrations in the distribution of different neurotrophic factors and in the expression of their receptors such as the brain-derived neurotrophic factor have been described in AD.

Neurofibrillary Tangles

Neurofibrillary tangles are insoluble twisted fibres found inside the brain's cell. These tangles consist primarily of a protein called tau, which forms part of a structure called a microtubule. The microtubule helps transport nutrients and other important substance from one part of thr nerve cell to another. In Alzheimer's disease, however, the tau protein is abnormal and the microtubule structures collapse.

DIAGNOSIS:

Patient History

It helps the doctor assess an individuals past and current health situation. It also helps the doctor evaluate any medical problems develop a plan of treatment.

A thorough patient history includes:

- Patient age and sex
- Chief compliment
- History of current illness
- Psychological history
- Mental status(memory, language)

Laboratory tests

Lumbar Puncture/Spinal tap

CT scan(computed tomography)

Magnetic resonance imaging (MRI)

Electroencephalography (EEG)

Electrocardiogram (ECG)

Neuropsychological testing

Stages of Alzheimer's disease:

Alzheimer's disease is the most common form of dementia in individuals older than 65years.

Alzheimer's progresses slowly in 3 stages:

- Stage 1: Mild/early (last 2-4 years)
- Stage 2: Moderate/middle (last 2-10 years)
- Stage 3: Severe/Late (last 1-3+ years)

Treatment:

Pharmacological treatment:

- **ACETYLCHOLINESTERASE INHIBITORS**
- The cholinesterase inhibitor tacrine (Cognex) is used rarely because of potential liver toxicity and the need for frequent laboratory monitoring. The acetylcholinesterase inhibitors donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl) have been proved effective in clinical trials. Table 1 compares the pharmacologic characteristics of the three acetylcholinesterase inhibitors and provides dosing and cost information

- **Acetylcholinesterase Inhibitors Used in the Treatment of** Alzheimer's Disease

Donepezil (Aricept)	Acetylcholinesterase Inhibitor	Start at 5 mg once daily, taken at bed time; after 6 weeks, increased to 10 mg once daily.	10 mg once daily	5 mg daily
Rivastigmine (Exelon)	Acetylcholinesterase Inhibitor (or) Butyrylcholinesterase inhibitor	Start at 1.5 mg Twice daily, Taken with food ; at 2 weeks intervals , increase each dose by 1.5mg.	6 mg twice daily	3 mg twice daily

CHANGES IN THE BRAIN:

Brain Basics

1.**Three pounds, three parts**

Brain is most powerful organ, yet weighs only about three pounds. It has a texture similar to firm jelly.

It has three main parts:

a) The cerebrum fills up most of the skull.It is involved in remembering, problem solving, thinking, and feeling. It also controls movement.

b) The cerebellum sits at the back of head,under the cerebrum.It controls coordination and balance.

c) The brain stem sits beneath cerebrum in front of cerebellum. It connects the brain to the spinal cord and controls automatic functions such as breathing, digestion, heart rate and blood pressure.

2.Supply lines

Brain is nourished by one of body's richest networks of blood vessles.With each heartbeat, arteries carry about 20 to 25% of blood to brain, where billions of cells use about 20% of the oxygen and fuel your blood carries.when we are thinking hard, our brain may use up to 50% of the fuel and oxygen

3.The cortex: "Thinking wrinkles"

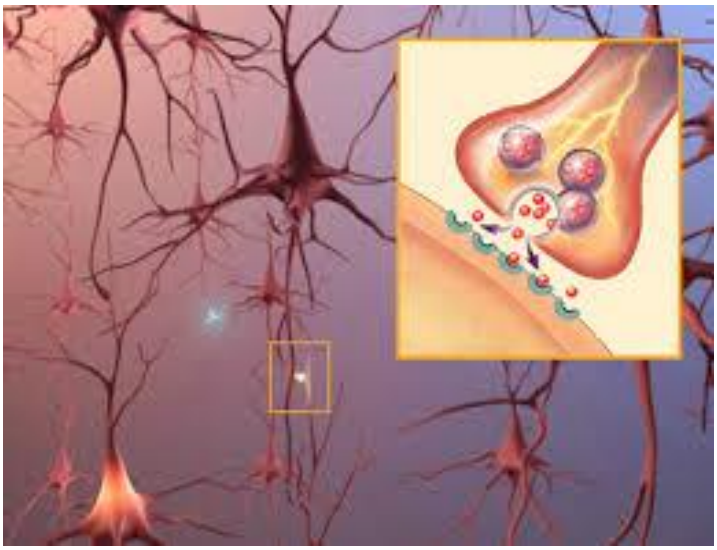
Brain's wrinkled surface is a specialized outer layer of the cerebrum called the cortex.Scientists have "mapped" the cortex by identifying areas strongly linked to certain functions.

4.The neuron forest

The real work of brain goes on in individual cells. An adult brain contains about 100 billions nerve cells, or neurons, with branches that connect at more than 100 trillion points. Scientists call this dense, branching network a "neuron forest".

Signals traveling through the neuron forest form the basis of memories, thoughts, and feelings.Neurons are the chief type of cell destroyed by Alzheimer's disease.

5.Cell signaling



Signals that form memories and thoughts move through an individual nerve cell as a tiny electrical charge.Nerve cells connect to one another at synapses. When a charge reaches a synapse, it may trigger realese of tiny bursts of chemicals called neurotransmitters. The neurotransmitters travel across the synapse, carrying signals to other cells. Scientists have identified dozens of neurotransmitters.

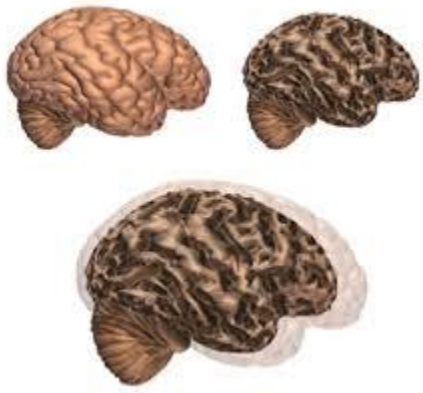
Alzheimer's disease distrupts both the way electrical charges travel within cells and the activity of neurotransmitters.

6.Signal coding

100 billion nerve cells… 100 trillion synapses….dozens of neurotransmitters…This "strength in numbers" provides brain's raw material. Over time, our experiences create patterns in signal type and strength. These patterns of activity explain how, at the cellular level, our brains code our thoughts, memories, skills and sense of who we are.
The position emission tomography(PET) scan in the above figure shows typical patterns of brain activity associated with:

a) Reading words
b) Hearing words
c) Thinking about words
d) Saying words

7.Alzheimer's changes the whole brain

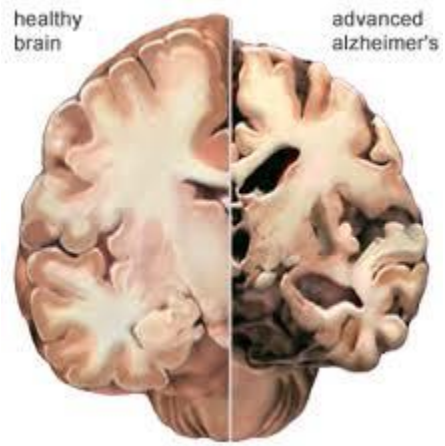


This images shows:

a) A brain without the disease
b) A brain with advanced Alzheimer's
c) How the two brains compare

8.More brain changes

Here is another view of how massive cell loss changes the whole brain in advanced Alzheimer's disease. This slide shows a crosswise "slice" through the middle of the brain between the ears.



In the Alzheimer's brain:

A. The cortex shrivels up, damaging areas involved in thinking, planning and remembering.
B. Shrinkage is especially severe in the hippocampus, an area of the cortex that plays a key role in formation of new memories.
C. Ventricles (fluid filled spaces within the brain)grow larger.

9.Under microscope

Scientists can also see the terrible effects of alzheimer's disease when they look at brain tissue under the microscope:

a) Alzheimer tissue has many fewer nerve cells and synapses than a healthy brain.
b) Plaques, abnormal clusters of protein fragments, build up between nerve cells.
c) Dead and dying nerve cells contain tangles, which are made up of twisted strands of another protein.

10.Earliest Alzheimer stages

In the earliest stages, before symptoms can be dected with current tests, plaques and tangles begin to form in brain areas involved in:

a) Learning and memory
b) Thinking and planning

CONCLUSION:

Alzheimer's disease is an irreversible, progressive brain disease that slowly destroys memory and thinking skills. The prevalence is 3% for persons 65-74 years old, 19% for those 75-84 years pld and 47% for those over 85 years old. Ad is mainly clinically manifested with dementia. The etiology of AD includes cholinergic, amyloid, tau hypothesis. Pathogenesis of AD involves the apperance of extra cellular beta-amyloid plaques and intra cellular neurofibrillary tangles. Drugs mainly includes Anticholinesterases. The recent reserchers using various animal modles are promising a definite and complete treatment for AD in coming years. Above everything it is the love and affection of the family that is what required for AD patient. Alzheimer's patients are exactly like any other patients in that they need plenty of care, support, patience, and love.

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