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Review on Alzheimer's disease: past, present and future

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Abstract

Alzheimer's disease is a progressive neurodegenerative disorders that is the six leading Cause of death and the most common cause of dementia worldwide. The most common cause of dementia is Alzheimer's disease (AD). Accounting for nearly 60 to 80 % of all cases. AD is the six leading cause of death with an estimated prevalence of nearly 30 million people worldwide. Age is the most important risk factor for AD, with an exponential increase in prevalence from 3 to 32 % from the ages 65 to 85 years old. An estimated 5.6 million individuals over the age of 65 suffer from AD in the United States, a number projected to nearly triple to 13.8 million by 2050 due to increase in population. The 2000s ushered in a focus on the study of prodromal stages of neurodegerative disease before the full – blown dementia syndrome. The current decades have been the rise of imaging and other biomarkers to characterize preclinical disease before the development of significant cognitive decline. Finally, we suggest future directions and predictions for dementia related research and potential therapeuticinterventions.

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Introduction

Alzheimer's disease (AD) named after the German psychiatric Alois Alzheimer is the most common type of dementia and can be defined as a slowly progressive neurodegenerative disease characterized by neurotic plaques and neurofibrillary tangles as a result of amyloid-beta peptides accumulation in the most affected area of the brain, the medial temporal lobe and neocortical structures [2]. This classification was essentially adopted by the American Psychiatric Association (APA) to define dementia in the first two editions of their Diagnostic and Statistical Manual of Mental Disorders (DSM). Specifically, DSM-II defined 'Organic brain syndrome" as a "basic mental condition characteristically resulting from diffuse impairment of brain tissue function from whatever cause", and which is manifested behaviourally as impairment in orientation, memory, intellectual functions, judgment [3]. Alzheimer's disease (AD) is the utmost common form of dementia, a usual term for memory defect and other cognitive impairments that seriously affect daily life. This degenerative disease is accountable for 60-80% of dementia cases. AD is not a typical part of normal aging. The supreme well- known threatening factor is aging, and the mainstream of people with AD are 65 years and older. In fact, AD is not considered as a disease of adulthood. AD and other typed of dementia affect a predictable 1 in 14 persons over the 65 year of age and 1 in every 6 persons over 80 years of age. But, about 1 in every 20 cases of AD affects people with in age ranging 40-65 years, which is called early-onset AD. AD is a progressive disease that deteriorates over time, and symptoms of dementia steadily exacerbate. In its initial stages, memory defect is mild, but over a number of years in late-stage, AD patients lose the aptitude to convey a message and reply to their surroundings. AD is the sixth foremost cause of death in the USA. Patients with AD may live an average of 8 years

After the symptoms are visible to others, but the survival rate is higher; it can

Etiology

The prevalence of dementia in the United States in individuals aged 65 years or older is about 8%. With these rates doubling those with milder forms of dementia or cognitive impairment are included. Rated of dementia are very much age dependent doubling every 5 years from 1% to 2% at ages 65 to 70 years, 30% and higher after the age 85 years [19]. The cause and development of the disease is idiopathic causes of disease. Acquired deficiency of acetylcholine and its enzymes in the structures of the cerebral cortex amyloid deposits are defected in senile plaques, brain vessels and membranes, as well as in vascular plexuses. It is represented by 4CD- a protein, is localized on chromosome [21]. Symptoms: Early signs and symptoms of Alzheimer's dementia include:

- Memory impairment, such as difficulty remembering events.
- Difficulty concentrating, planning or problem-solving
- Problems finishing daily tasks at work
- Confusion with location or passage of time
- Having visual or space difficulties, such a not understanding distance in driving, getting lost or misplacing items
- language problems, such as word-finding problems or reduced vocabulary in speech or writing
- Using poor judgment in decisions
- Withdrawal from work events or social engagements
- Changes in mood, such as depressions or other depressions or other behavior and personality changes.

Diagnosis

A patient suspected to have AD should undergo several tests, including neurological examinations such as vitamin B12 and other tests besides the medical and family history of the patients [20]. Neuropsychological tests, progressive memory loss, impaired daily-life activity and other symptoms like Aphasia and Agnosia. All these symptoms can start from 40-90 with absence of any systemic or brain diseases. AD is both a clinical and a neuropathological entity, the definitive diagnosis of AD can be made only with a brain biopsy or an autopsy. One of the major clinical advances in the diagnosis of AD has been the promulgation of diagnostic criteria for possible and probable AD by a select group sponsored by the National Institute of Neurological and related and communicative disorders and stroke- Alzheimer's disease and related disorders Association. Using these criteria, the clinical diagnosis of AD Has been confirmed at autopsy in close to 90% of cases. It has been stated that AD is a diagnosis of exclusion. This is only partially correct.

- Psychiatric assessments.
- Mental status examination and neuro psychological assessment
- Laboratory tests.
- Brain imaging
- CT scan
- MRI
- PET
- SPECT
- CSF Examination
- Electromyogram

Causes and risk factors

AS has been considered a multifactorial disease associated with several risk factors, 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 (Alpha beta, 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 impairment in the cholinergic function is a critical risk factor for AD, while others suggest that alteration in amyloidal β-protein production and processing is the main initiating factor. However, at present, there is no accepted theory for explaining the AD pathogenesis [15-16].

Stages

stage 1-

- Normal Mentally healthy person.

Stage 2

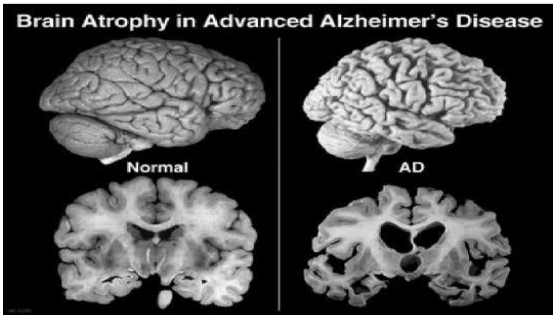
- Normal aged forgetfulness Persons over the age of 65 experience subjective complaints of cognitive or functional difficulties.

Stage 3

- Mild cognitive impairment the capacity to perform executive functions also becomes compromise.

Stage 4

- Mild Alzheimer's disease the most common functioning deficit in his patience is a decreased ability to manage instrumental activities of daily life.



Clinical phases of Alzheimer's disease can be classified into pre-clinical or the pre-symptomatic stage, which can last for several years or more. This stage is characterized by mild memory loss and early pathological changes in cortex and hippocampus, with no functional impairment in the daily activities and absence of clinical signs and symptoms of AD. The mild or early stage of AD, where several symptoms start to appear in patients, such as a trouble in the daily life of the patient with a loss of concentration and memory, disorientation of place and time, a change in the mood, and a development of depression. Moderate AD stage, in which the disease spreads to cerebral cortex areas that results in an increased memory loss with trouble recognizing family and friends, a loss of impulse control, and difficulty in reading, writing, and speaking. Severe AD or late-stage, which involves the spread of the disease to the entire cortex area with a severe accumulation of neurotic plaques and neurofibrillary tangles, resulting in a progressive functional and cognitive impairment where the patients cannot recognize their family at all and may become bedridden with difficulties in swallowing and urination, and eventually leading to the patient's death due to these complications [5, 6].

Pathophysiology

The deposition of tangles follows a defined pattern, starting from the trans-entorhinal cortex; consequently the entorhinal cortex, the CA1 region of the hippocampus and then the cortical association areas, where frontal, parietal and temporal lobes are particularly affected. The extent and placement of tangle formation correlates well with the severity of dementia, much more so than numbers of amyloid plaques [7]. The accretion of tau proteins correlates very closely with cognitive decline and brain atrophy, including hippocampal atrophy. In the neuropathology of Alzheimer's disease there is a loss of neurons and atrophy in temporofrontal cortex, which causes inflammation and deposit the amyloid plaques and an abnormal cluster of protein fragments and tangled bundles of fibres due to this there is an increase in the presence of monocytes and macrophages in cerebral cortex and it also activates the microglial cells in the parenchyma [9]. However, these can only relieve symptoms and not delay the progress of AD. Moreover, three cholinesterase inhibitors, namely, donepezil, rivastigmine, and galantamine, which are approved by the US Food and Drug Administration, were proven to increase side effects, such as nausea, vomiting, and diarrhea. Although the NMDA receptor antagonist memantine showed good effects on improving cognitive function and behavioural disturbance scores, it causes severe hypotension, leading to fainting, and falls. According to amyloid cascade theory (one of the most accepted theories about AD pathogenesis, although still debated), the cerebral accumulation of Aβ peptide, resulting from the imbalance between production and clearance of this protein, is the main event causing the disease, being other events observed (including the formation of NFT) resulting from this process. As a result of this process, damage to neurons and synapses involved in memory processes, learning and other cognitive functions lead to the aforementioned cognitive decline.

Treatment

Aducanumab is only disease modifying medication currently approved to treat Alzheimer's this medication is a human body, or immune therapy that targets the protein beta. Amyloid and helps to reduce Amyloid, plaques which are brain lessons associated with Alzheimer's.

Cholinesterase Inhibitors: According to the cholinergic hypothesis, AD is due to the reduction in acetylcholine (acH) biosynthesis.

- Donepezil
- Rivastigmine

Drug	Type of inhibition	Duration of action and dosage	Side effects
Tacrine	Not CNS selective	~6 h 2-3 times daily oral dosage	Cholinergic side effects hepatotoxicity Monitoring for hepatotoxicity needed
Donepezil	CNS, AChE selective	~24 h Once-daily oral dosage	Slight cholinergic side effects
Rivastigmine	CNS selective	~8 h Twice-daily oral dosage	Cholinergic side effects that tend to subside with continuing treatment
Galantamine	Affects both AChE and BuChE Also enhances nicotinic ACh receptor activation by allosteric action	~8 h Twice-daily oral dosage	Slight cholinergic side effects

Conclusion

The most common genetic risk factor for AD is the epsilon 4 allele of the gene for apolipoprotein E (ApoE). Apart from the genetic and molecular aspect vitamin D deficient diet, active form of which regulates nerve growth factor seems to be another cause of AD.

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