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A concise description of Alzheimer's disease

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Abstract
Alzheimer's disease is irreversible damage and progressive nervous tissue disorder that gradually destroy memory, judgment and thinking capabilities and, ultimately, leads to loss in the ability of performing the simplest jobs. Person with Alzheimer's, exhibits symptoms in their mid-60s age. It is currently ranked as the seventh leading reason of death in the world. By 2050, more than 140 lakh aged US citizens are statically expected to face Alzheimer's disorder. Countless experiments have been performed to evaluate abnormal chemical, physical or electrical changes in brain so as to detect Alzheimer. Elevated death rates, enormous expenses for diagnosis along with cure, and patients' care, are among few consequences of this dreaded disease. Currently, no therapy is available for Alzheimer. A timely diagnosis assists in attaining essential support, suitable medication, and continuation, as much as possible, of involvement in intellectual, public, and physical behaviors. Furthermore, early detection also provides the opportunity to start treatment before neurodegeneration has progressed and with only minimal disease pathology present. This is really effective for improving the life quality of the patients and their family members. Therefore, in the present paper, authors have presented a brief overview of the disease along with its treatment options so that the patients might get optimum health care at an early stage to continue a serene life.

Keywords: Alzheimer, ageing, cognition, dementia, multi-component diet, neurodegeneration

Introduction
Alzheimer is an occasional age-related neurodegenerative disorder, whose occurrence is escalating worldwide [1]. This disorder is characterized by cognitive and emotional impairments, which develop through the years. It leads to accumulation of the some abnormal proteins like beta-amyloid and phosphorylated tau, which has negative neurodegeneration effects [2]. The neurological changes in Alzheimer's condition leads to dementia. Toxic variations in the brain gradually destroy memories, languages and thinking capability. Symptoms mainly first appear in the age of mid-60s [3]. General symptoms are the decline of memory, reasoning, language, and perceptual interpretation, which affect daily functioning and the quality of life [4].The disorder gets worse over time passing and ultimately leads to failure of brain function. One of the first noticeable symptoms among Alzheimer's patients is the loss of episodic memories and the difficulties of learning new information [5]. As Alzheimer progresses, patients experience larger memory loss, cognitive impairments and behavioral changes. Typical problems comprise wandering and getting lost; being suspicious about family and caregivers; taking larger time to complete daily tasks; or, not being able to speak, write and walk properly [6]. Currently, when Alzheimer's disease is diagnosed, the neuronal damage is spread enough to make it irreversible. When neurons die, the other neurons do not segregate to replace them, therefore, this damage is not reversed [7]. The two proteins that primarily destroy the brain activity includes called beta-amyloid and tau. Beta-amyloid protein clumps/binds into plaques, which gradually accumulate between brain cells. Abnormal protein tau builds up within brain cells, forming tangles [8]. These tangles and plaques condition in the nerve or brain cells are characteristics of Alzheimer's disease. Another symptom is the loss of associations among nerve cells. It affects diverse parts of the brain, and from the brain to muscles cells and various organs in the body [9]. A lot of additional compound neuron changes are consideration to play a significant role in Alzheimer's, too. This damage leads to loss in memory, counting the entorhinal cortex region and hippocampus area [10].

It later acts on cerebral cortex, for instance leads to impairment in language interpretation, reasoning capability, and social behavior. Eventually, leads to other main areas of the brain are damaged. Alzheimer's patients also face a deficiency of chemical messengers that function is to transmit signals around the body and brain [11]. Treatments for Alzheimer's disease can boost the number of various chemical messengers in the brain, which can assist among a number of the symptoms. Alzheimer's is a progressive disorder that gradually, leads to damaging of brain. As this happens, more and more symptoms develop and diseases become more severe [12].

Mild Alzheimer's disease

As Alzheimer's disorder continue patient facing greater loss in memory and other cognitive complexity. The main problems can face in these conditions is wandering and getting lost, difficulty in handling currency and in paying bills, repeating a lots of questions, taking larger time to complete ordinary day by day tasks, personality and behavior losses[13]. Patients are frequently diagnosed at this initial stage.

Moderate Alzheimer's disease

During this point, loss occurs in those regions of the brain that assist language control, reasoning interpretation, processing of sensory message and various conscious thinking. Greater loss in memory and confusion grow to worst level, and patients start to have problems in recognizing family members [14].

Severe Alzheimer's disease

Eventually, plaques and tangles reach to each part of the brain, and nerve tissue shrinks considerably. Patient with severe condition of Alzheimer's cannot communicate and are totally dependent on others people for their nursing. Near the last days, the patient might be in bed in most or all of the occasion as the patient body shuts down [15].

What Causes Alzheimer's?

Researchers don't yet completely recognize what causes Alzheimer's disorder in the majority of patients. Genetic mutation is one of the causes of early-ons*et al*zheimer disorder. A complex series of brain changes is one of the major reasons for Late-ons*et al*zheimer's. The causes probably include a combination of genetic, environmental, and lifestyle factors [16]. The contribution of any one of these causes in enhancing or declining the danger of emerging Alzheimer's may vary from person to person. Mutations in three genes are also a reason for mutation: the amyloid protein, presenilin 1 and presenilin 2, present on chromosomes number 21, 14 and 1 respectively [17]. For old age Alzheimer's disorder, the genetic risk protein is Apo E, present on chromosome number 19. Three gene or allele exist (ApoE e2, ApoE e3, and ApoE e4), with possession of single e4 gene being linked with a 3 times more risk for the expansion of Alzheimer's disorder, whereas homozygous genetic makeup have an 8 times more risk [18].

Clinical Aspects of AD

Amnesia is first sign of Alzheimer. A decline in other aspects of thinking, such as communication, vision/spatial impairment and damaged reasoning or judgment, may also signal the very early stages of Alzheimer's disease. Mild cognitive impairment might be an early sign of Alzheimer's, but not in every individual [19].

Initial symptoms

They affect nearly all composite activities of an individual. The most noticeable short-term memory loss is the most common effect in which an individual is uncertain about the new learned facts and information [19]. Attentiveness, abstract thinking and planning are also impaired. It could lead to depression and apathy [20]. Early stage symptoms are collectively termed as mild cognitive impairment (MCI), consequently leading to amnestic MCI.

Early stage

The enhancement in memory impairment sooner or later results in complications such as agnosia and apraxia Alzheimer's disease does not affect all memory capacities equally. Episodic semantic and implicit memory are least affected. Contraction in vocabulary and dwindling fluency are the main language problems associated with early stage of AD. Individuals of this stage generally get unnoticed as they are capable of performing most of their tasks adequately. With the progression of disease they sometimes require support or supervision [21].

Middle stage

Progressive worsening in due course holds back independence as the person at this stage is unable to perform usual commotions of daily basis. Speech deterioration becomes evident leading to paraphasias. Reading and writing skills become less coordinated, complex motor sequences are progressively lost leading to increase risk of falling [22].An individual fails to recognize family members and close relatives. Long-term memory is impaired. Urinary incontinence might develop. Emotional instability, irritability, aggression and other neuropsychiatric problems develop ultimately causing stress to caregivers.

Final stage

During the severe stage, an individual is totally dependent on caregivers. Language declines to single words and ultimately loosing speech. Aggressiveness worsens leading to intense apathy and exhaustion [23]. Muscle content and locomotion declines and individuals become so bed ridden that they have to be fed. This is also called terminal stage as it results in death.

Pathophysiology of AD

Amyloid hypothesis

Proteolytic cleavage of the amyloid precursor protein (APP) by enzymes secretase produce Amyloid beta as end product. The final piece of the amyloid beta protein (cleaved by β and γ-secretase) is reliant on first cleavage of the extracellular domain resulting in the amyloidogenic end products (Aβ 1-42 and Aβ 1-40), [24]. Aβ 1-42 is highly neurotoxic forming senile plaques [25]. Also, the ratio between soluble Aβ 1-42 and Aβ 1-40 in cerebrospinal fluid correlates directly with the age of onset of AD [26]. Thus, imbalance between generation and clearance of Aβ leads in augmentation of Aβ that initiates a pattern of subsequent pathological changes. These include failure in synapses and neurons, impaired glucose utility, brain metabolic reduction, oxidative damage, tau protein hyper phosphorylation and correlated neurofibrillary tangle formation. This complex cascade of pathological affairs continues throughout the course of AD, leading to an accumulation of structural and functional cerebral damages, causing the typical clinical symptoms of the disease [27].

Tau Hypothesis

Tau is a protein found in axons and dendrites. It promotes tubulin polymerization and stabilizes microtubules. Thus, it crucial in formation of cell structure and cellular transport [28]. In addition, Tau is engaged in axonal growth. But, its excessive phosphorylation prevents its binding to microtubules, causing destabilization of cell structure. This results in to axonal, dendritic and synaptic loss [29]. Presence of these neurofibrillary lesions is characteristic of AD.

Acetylcholine hypothesis

Cholinergic neurons of basal forebrain innervate the hippocampus and neocortex. Both these regions show high densities of plaques along with tangles leading to loss of cognitive function in AD [30]. It has been shown that Aβ peptides have acute negative effects on formation and discharge of acetylcholine (ACh). Furthermore, the adverse effects of Aβ, emerge to be discriminating for cholinergic neurons [31]. Tau proteins also come out to be vital for the Aβ induced neurotoxicity, linking the two pathological traits of AD, to the loss of cholinergic neurons and decline in cognitive function. Hence, a shift in the balance between cholinergic innervations and Aβ may be a key factor in early targeting of cholinergic neurons in AD [32]. Certainly, the density of synaptic terminals containing choline acetyl transferase (ACh synthesizing enzyme) in the neocortex is distorted early in the AD process [33].

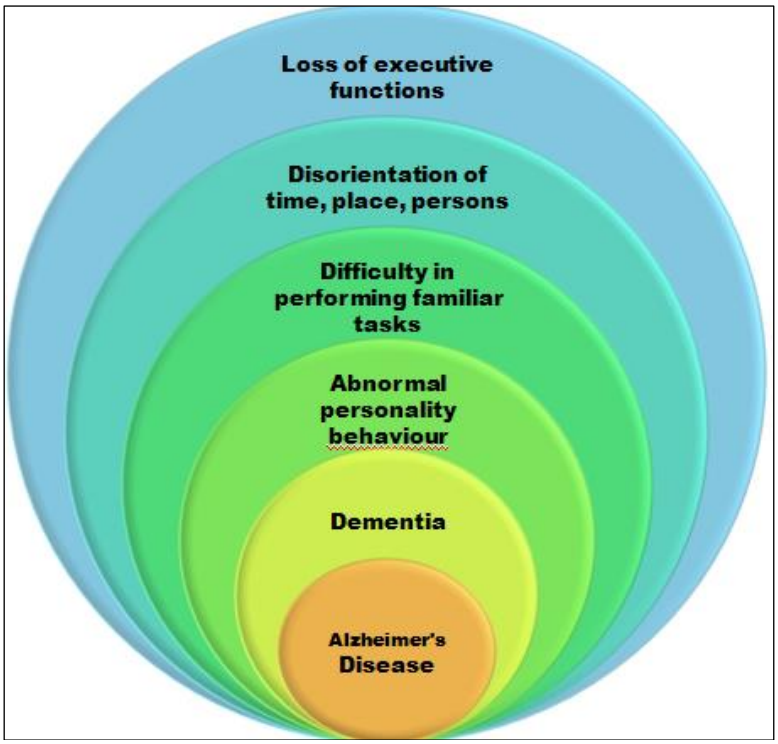

Fig 1: Clinical Signs of AD

Ageing

The standard aging process is generally linked with a gradual neuronal loss, lesser capacity of brain to create new synapses and various biochemical changes at the membrane level. These biochemical alterations influence axonal signal transduction, regulation of membrane bound enzymes, ion channel structure and maintenance of various receptors [34]. Furthermore, cellular membrane undergoing ageing is described by elevation in cholesterol, and low content of PUFA (poly unsaturated fatty acids). This is a consequence of poor uptake of PUF. As over the blood-brain barrier, declined integration into the membrane and decreased enzymatic activity [35]. Also, cerebral blood stream decreases with aging and is associated with a loss of endothelial function, the decline being more pronounced in AD patients.

Table 1: Risk Factors

Down syndrome	Related to having three copies of chromosome 21and subsequently three copies of the gene for the protein that leads to the creation of beta-amyloid [33]
Sex	Overall, there are more women with the disease [36]
Mild cognitive impairment	When the primary MCI deficit is memory, the condition is more likely to progress to dementia due to Alzheimer's disease [37]
Head trauma	Several research confirmed that people age 50 years or older who had a traumatic brain injury (TBI), there is increased risk of dementia and Alzheimer's disease [38]
Air pollution	Human studies have found that air pollution exposure particularly from traffic exhaust and burning wood is associated with greater dementia risk [39]
Excessive alcohol consumption	Drinking large amounts of alcohol has long been known to cause brain changes [31]
Poor sleep patterns	Difficulty falling asleep or staying asleep, are associated with an increased risk of Alzheimer's disease [40]
Lifestyle and heart health	Lack of exercise, Obesity, Smoking or exposure to secondhand smoke, High blood pressure, High cholesterol, poorly controlled type 2 diabetes [41]

Treatment of AD

Current FDA approved Alzheimer's medications help to aid memory symptoms and other cognitive changes [42, 43]. The types of drugs that are currently used to treat cognitive symptoms include the following.

1. Cholinesterase inhibitors: Cholinesterase inhibitors boost neuronal content of acetylcholine by preventing its collapse in the nervous tissue [44]. These drugs function by boosting levels of communication by preserving Acetylcholine. These are usually the first medications tried, and the majority of people see modest improvements in symptoms. They may also improve depression. Commonly prescribed cholinesterase inhibitors include Aricept (donepezil), Razadyne ER (galantamine) and Exelon (rivastigmine) [45]. Donepezilis used to treat all stages of the disease. It's taken O.D in the form of a pill [46]. Galantamineand Rivastigmine are approved for treating mild to moderate Alzheimer's [47]. Taken as a pill once a day or as an extended release capsule twice a day. The adverse effects of these drugs include loss of appetite, diarrhea, nausea and sleep disturbances.
2. Memantine (Namenda).It works in brain cell communication scheme and slows the succession of symptoms with modest to relentless Alzheimer's disease [48]. It is used along with a cholinesterase inhibitor. Relatively rare side effects include dizziness and confusion.
3. In last year, June 2021, US FDA approved Aduhelm (aducanumab) for treating some cases of Alzheimer's disease by removing amyloid plaques in the brain [48].
4. Few medications for example antidepressant drugs might prove helpful in controlling the behavioral symptoms associated with AD [49].

All these treatmentsare not capable to reverse Alzheimer's disorder or prevent the destruction of nervous tissue. Ultimately, they drop efficiency because deteriorating nerve cells synthesize low levels of acetylcholine as the disorder progresses [50].

Role of dietary components in AD

Alzheimer patients are found to be deficient in specific nutrients. Low intake of these nutrients is being associated with raised risk of developing AD [51]. Deleterious dietetic habits such as overconsumption, lofty caloric/squat dietary fibre diet or eating of less antioxidant nutrients), sedentary lifestyle and stress, is accounted as particular factors resulting in oxidative trauma and brain disorders [33]. Specific nutrient concentrations in the cerebrospinal fluid are influenced by Blood Brain Barrier (BBB) integrity, which aggravate the prognosis in AD. Another study has demonstrated that BBB function is modifiable through vitamin therapies [52]. Endothelial cells form a critical part of the BBB and are actively engaged in the transport of nutrients to the brain via blood. Thus, dysfunction of endothelial cells along with the BBB may contribute to inadequate supply of nutrients and energy to brain [53]. Also, reduced metabolism of brain glucose has been reported in AD patients with mild cognitive impairment, the preclinical stage of Alzheimer Disease, and inhibition of energy metabolism may increase amyloidogenic meting out of APP [54]. Growing preclinical plus clinical research in healthy individuals or at the early stage of cognitive decline has demonstrated the beneficial impact of nutrition on cognitive functions [55]. It is well known reality that the proportion of elderly populations will increase dramatically in almost every country in the next few decades. Numerous epidemiological studies indicate that continuing intake of fruits, vegetables, legumes correlates with better cognition [56]. Thus, maintaining health of BBB may be one target for nutritional therapies, intended to maintain cognitive function.

Nutrition may represent a promising strategy for lifestyle-based preventive interventions against dementia along with AD [57]. The formation over and above maintenance of new neuronal membrane composition is highly dynamic processes that occur continuously throughout life. For this various precursors and vital building blocks are needed, which are largely provided via the diet. For instance, the rate of synthesis of neurotransmitters such as ACh is also dependent on dietary intake of precursors. Biosynthesis of acetylcholine is controlled by dietary intake of choline [58]. Choline supplementation increases acetylcholine release. Several dietary components, acting as antioxidant, anti-inflammatory and/or insulin action potentiating factors, could positively participate in a preventive nutritional approach to healthy ageing of brain [59]. This might enable the prevention or delay of diseases and increase eminence of life in the elderly [60]. Thus, diet is currently considered a vital factor for managing degenerative diseases like AD.

Micronutrients

Polyunsaturated Omega 3 fatty acids Long-chain PUFAs (Polyunsaturated fatty acids), EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) are linked with decreased brain inflammation plus preservation of the integrity and function of neurilemma [61]. DHA is a key component of phospholipid membranes and modulate the APP, thereby reducing formation and increasing clearance of amyloid plaques [33].

Vitamins

Among vitamins, high dietary intakes of tocopherols (Vitamin E) are linked with a minuscule risk of AD [62]. Clinical evidence has demonstrated a correlation between raised plasma homocysteine (Hcy) and the occurrence of AD [32]. The mechanisms that support the relation between vitamins B along with the brain are mostly related to homocysteine (Hcy) metabolism, which is a marker of vitamin B insufficiency. Vitamin D also has a major role in brain development, maturation, and functioning [63]. Furthermore, all these non-polar nutrients exhibit potential anti amyloid action along with potent anti-inflammatory and antioxidant properties. This aids in lowering neuroinflammation in addition to oxidative stress correlated with dementia and AD [64].

Zinc

Zn acts optimistically on brain health. It improves insulin sensitivity and reduces inflammatory cascade as well as oxidative stress [65].

Polyphenols

Recent studies exhibit protective associations between dietary polyphenols and the prevention of age-related chronic diseases such as diabetes, cancers, osteoporosis and neurodegenerative diseases like AD [32].

Flavonoids

Flavonoids, is a constituent of number of fruits, vegetables and various beverages, have been identified as promising agents capable of influencing diverse aspects of synaptic plasticity leading to developments in memory and learning in both animals and humans [54]. Flavonoids induced improvements in spatial memory in animal models is already reported in literature [52]. They are much more likely to combat neuronal dysfunction and toxicity by recruiting anti-apoptotic pro-survival signalling pathways, increasing antioxidant gene expression and reducing amyloid beta pathology [33].

Conclusion

AD is a neurodegenerative disorder that ultimately imparts negative impact on a person's capability to live independently. There are various forms of dementia, even though Alzheimer's disorder is the most common type. While patients with dementia condition frequently exhibit behaviors that are difficult for family members and professional caregivers to direct, the behaviors are caused by damage to the brain and are not intentional. Challenging behaviors can be caused by unmet needs and may be a means of communication. By carefully observing what comes directly before and after a behavior, the caregiver may be able to determine the underlying need and learn how to alleviate the challenging behavior. People with dementia need to be treated with kindness and with the knowledge that they can still enjoy life.

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