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Review Article

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Up in Arms against Alzheimer's Disease

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Abstract

Memory is an ability of the human brain to retain and store diverse learned experiences, those can be recalled using as per the requirement of an individual. Memory goes hand in hand with forgetting that is a normal phenomenon and safeguards brain from getting oversaturated with the not very relevant information's. Amnesia is impaired ability to form and remember new information and/or to recall past events. Dementia is one of the most important causes of amnesia and other cognitive deficiencies and Alzheimer's disease is one of the most significant causes of Dementia. German psychiatrist and neuropathologist Alois Alzheimer in 1906 first time recognized this disease during the brain autopsy of her patient Auguste Deter.

There are now 46.8 million people (5-6%) living with dementia worldwide. One of the hallmarks of Alzheimer's disease is the accumulation of amyloid plaques between nerve cells (inter-neuronal) in the brain. There is also deposition of neurofibrillary tangles of Tau proteins as insoluble twisted fibers inside the brain's nerve cells. These plaques and tangles destroys axon terminals and dendrites of several neurons and synapses, causing severe disconnection, shrinkage and atrophy of brain. There is no definite single test, but Alzheimer's could usually be diagnosed through a systematic assessment i.e.,thorough medical history for symptoms from the patients & collateral history from relatives, a physical and neurological examination to rule out other neurological disorders, presence of risk factors, neuropsychometric assessment for scaling cognitive functions, Smell Test, Brain imaging- CT, fMRI and PET and Cerebrospinal Fluid (CSF) assays. There is no definite cure for AD, but treatment by two types of drugs is currently used to allay cognitive symptoms, one type is cholinesterase inhibitors and second type is glutamatergic partial antagonist. Ultimately, prevention through a holistic approach is need of hour. In India, awareness for Alzheimer's disease is also essential at this instant, specifically in view of increased life span.

Keywords: Amnesia; Alzheimer's Disease; AD; Dementia

Introduction

Memory [1]

This is an ability of the human brain to retain and store diverse learned experiences, those can be recalled using as per the requirement of an individual. From a physiologic point of view, memory is divided into explicit and implicit memory forms. Explicit or declarative memory is associated with awareness and is for factual knowledge about people, places, things (Semantic) and event experiences (episodic). It is dependent on the hippocampus and other parts of medial temporal lobes and prefrontal cortex for its retention. Implicit or non-declarative memory is not associated with awareness and is for training reflexive motor or perceptual skills. Retention of implicit memory does not usually involve processing in the hippocampus but other brain areas as neocortex, motor cortex, basal ganglia, cerebellum and amygdale are basically involved. Implicit memory initially requires some explicit memory for activities to learn like riding a bicycle.

Stages of Memory (Atkinson-Shiffrin Model or Multi-Store Model) [2]

Information is detected by various sense organs (eyes, ears,

nasal epithelium, taste buds etc.) and enters the Sensory Memory (SM). If attended to this information enters the Short-Term Memory (STM). Information from the STM is transferred to the Long-Term Memory (LTM) only if that information is rehearsed. Thus, human memory has three separate stages:

- Sensory Memory (SM): When an environmental stimulus is detected by a sense, it is very briefly available or registered for multiple senses. The duration of sensory memory is¼ to ½ second and capacity is for all sensory experience.
- Short-Term Memory (STM): This receives and holds inputs from the sensory register or record to get encoded and consolidated later to become Long Term Memory (LTM). The duration of STM is 0 to18 seconds and capacity is for 7 +/- 2 items.
- Long-Term Memory (LTM): Information, that has been rehearsed in the short-term store is held in long term memory indefinitely and can be retrieved as per need, the duration and capacity of this memory are unlimited.

Forgetting [3,4]

Forgetting is a protective and normal phenomenon to safeguard brains from getting oversaturated with the not very relevant information's. These are few causes of forgetting:

- Encoding and Consolidation failure.
- Decaying or Fading of memories over time.
- Inadequate retrieval cues.

Amnesia [5]

It is impaired ability to form and remember new information and/or to recall past events. There are two basic types of amnesia. These are defined based on the nature ofthe deficit, with respect to memories 'before vs. after' the accident that caused the amnesia.

The inability to remember events that occurred before the accident (recent past) is called retrograde amnesia. The inability to remember events that occur after the accident (or inability to form new memories) is referred to as anterograde amnesia. In terms of the multi-store model, retrograde amnesia isa deficit in retrieval, since this is the inability to retrieve information from long term memory that was already stored. On the other hand, anterograde amnesia is a deficit in storage, in that it is the inability to store new information into long term memory. Amnesia may be cured if the cause is treatable.

Causes of Amnesia [5]

Damage of certain parts of brain (important in the processing & retention of memory).

- Neuro Degenerative Disorders-Dementia.
- Stroke (involving Hippocampal injury).
- Brain inflammation.
- Oxygen deprivation in the brain.
- Bleeding within the brain tissue.
- Extreme alcohol intoxication.
- Seizures.
- Tumors.
- Statin drugs (used as treatment for hypercholesterolemia).
- Korsakoff's syndrome - excess use of alcohol.
- Head trauma, depression, drug interaction, thyroid problems and certain vitamin deficiencies i.e., thiamin (vitamin B1) deficiency.

Neuro-Degenerative Disorders-Dementia [6]

Dementia is a clinical syndrome or an umbrella term that covers following signs & symptoms:

- Difficulties in memory and other cognitive abilities like language, judgment, reasoning, planning and other thinking abilities.
- Psychological and psychiatric changes.
- Impairment in activities of daily living that usually first appears as memory weakness but later turns to be severe enough to interfere with daily life Examples: making a meal, paying bills, and travelling to a store to make a purchase.

Causes of Dementia [7]

- Alzheimer's disease (AD) is the most common cause of dementia (50% to70%).
- Vascular dementia occurs due to a series of small strokes.
- Lewy body dementia.
- Mixed dementia.
- Frontotemporal dementia.
- HIV-associated dementia.
- >65 years of age.
- Other treatable conditions that can cause dementia-like symptoms such as depression, adverse drug reaction, thyroid problems, excess use of alcohol or certain vitamin deficiencies i.e., thiamin(vitamin B1) deficiency.

Alzheimer's Disease (AD) [8]

German psychiatrist and neuropathologist Alois Alzheimer in 1906 first time recognized this disease during the brain autopsy of her patient Auguste Deter.

- Alzheimer's disease is the most common cause of dementia.
- A gradual onset disease causing an irreversible, progressive neurodegeneration, causing memory loss and other cognitive disability.

Prevalence [9]

There are now 46.8 million people (5-6%) living with de-

mentia worldwide, with numbers projected to nearly double every 20 years, increasing to 74.7 million by 2030 and 131.5 million by 2050.These estimates are 12-13% higher than those for the corresponding years in World Alzheimer Report 2009. Thus undoubtedly, it is a global health crisis condition. In India, more than 4 million people have some form of dementia. Today, the total estimated worldwide cost of dementia is US $818 billion. It will become a trillion-dollar disease by 2018.

Pathophysiology of Alzheimer's Disease (AD) [10-14]

A neuron is a nerve cell and brain is made up of approximately 100 billion neurons. Each individual neuron can form thousands of links with other neurons in this way, giving a typical brain well over 100 trillion synapses -to sense our environment, move, feel, think, reason, learn, remember, make decisions, plan, organize, communicate, solve problems, and create. Certain changes in brain during AD bring disruption of synaptic connections, functions and cause death and atrophy of neurons. There are following ways for causing brain atrophy:

One of the hallmarks of Alzheimer's Disease (AD) is the accumulation of β amyloid plaques between nerve cells (inter-neuronal) in the brain. β-Amyloid is a protein fragment and snipped of Amyloid Precursor Proteins (APP) and being sticky in nature, forms hard, insoluble plaques. APP is a transmembrane protein, important for neuronal growth, repair and survival. It has cleavage sites for two enzymes, beta secretase and gamma secretase. Pre-senilinsis the sub-component of gamma secretase that is responsible for the cutting of APP.In a healthy brain, these β amyloid protein fragments would break down and be eliminated. In Alzheimer's disease, the fragments accumulate to form hard, insoluble plaques. In AD patients, mutations in the Presenilin Proteins (PSEN1; PSEN2) or Amyloid Precursor Protein (APP) can be introduced. Gamma secretase can cleave APP at numerous places, which results in β amyloid of various lengths. The lengths associated with Alzheimer's disease are 40 and 42 amino acids long. Aβ 42 is more possibly form plaques in the brain than Aβ 40. Specifically, Presenilin mutations lead to an increase in the ratio of Aβ 42 produced compared to Aβ 40, although the total magnitude of Aβ produced may still be constant. This can come about by various effects of the mutations upon gamma secretase.

Neurofibrillary tangles are formed as insoluble twisted fibers inside the brain's nerve cells. They primarily consist of a protein called Tau, which forms part of a structure and holds the microtubules together. The microtubules help transport nutrients and other important substances like Neurotransmitters from one part of the nerve cell to another within axons. The Tau protein undergoes a chemical change called hyper phosphorylation and forms insoluble Neurofibrillary tangles thus causing collapse of microtubule structures. These changes bring destruction of synaptic connections and atrophy & death of neurons. These changes bring disruption of synaptic connections, function and cause atrophy & death of neurons. These plaques and Tangles destroys axon terminals and dendrites of several neurons and synapses, causing severe disconnection, shrinkage and atrophy of brain, and thus dilatation of the lateral ventricles .First in, the Entorhinal region-new memory processing center & retrieving old ones, they appear higher, in Hippocampus that forms complex memories and finally they reach the top of the brain, or Neocortex, the "executive" region that coordinate all cognitive functions thus effect thinking, planning, learning and memory, causing dependency, immobility, morbidity and death.

Alzheimer's disease is one of the neurodegenerative diseases that displays change in neurotransmitters, throughout the brain regions, those are implicated in cognition and emotions. In this disease, an imbalance between neurotransmitters, acetylcholine, glutamate, serotonin, dopamine, noradrenaline, GABA and many others are included. It has been suggested that the deterioration of memory and cognitive functions seen in AD patients is a consequence of the progressive degeneration of cholinergic neurons ofthe basal forebrain and the loss of cholinergic transmission in the hippocampus and cerebral cortex. The current drug therapy in AD patients that increase availability of Ach, by inhibitingacetylcholine-esterase enzyme, namely physostigmine, tacrine, and newly donepezil, rivastigmineand galantamine strongly indicate gradual loss of cholinergic neurons. Further, recently dysfunction of glutamatergic transmission has been identified as a distinctive process responsible for degeneration in AD as a drug that targets glutamate (glutamate antagonist, uncompetitive NMDA receptor antagonist rather than Ach), namely memantine, was introduced for the treatment of dementia. Glutamate (Glu) is one of the major excitatory neurotransmitters in the brainand spinal cord, and is of critical importance for learning and cognitive processes. In AD, due to the effects of Aβ peptides, glutamatergic neurons however activity, releasing glutamate continuously and in greateramounts compared to non-AD subjects, and the NMDA receptor is more sensitive in the course of AD thus displaying huge glutamatergic dysfunction. In brain examinations of AD patients, serotonin levels and the specific receptors are found to be decreased in the hippocampus and prefrontal cortex, serotonin levels are related with cognitive functions, whereas in the brainstem serotonin levels are related with mood. Psychotic symptoms, i.e. paranoia or hallucinations which can occur in patients with AD are associated with dopamine and serotonin hyperactivity in brain regions responsible for memory and emotions i.e., the mesolimbic system and hippocampus.

Neuro-inflammation: Recent data have identified the inflammatory processes usually caused byToxic metabolites, Autoimmunity, Aging, Microbes, Traumatic brain injury, Air pollution, Passive smokeas being closely linked with multiple neurodegenerative pathways. APP is an acute phase protein which is released in brain tissue following trauma and other insults causing neuroinflammation. The effects of neuroinflammation are mediated by activated microglial cells which are a source of cytokines and a potent gen-

erator of free radicals, complement components and pro-inflammatory agents. Advanced molecular studies have revealed multiple aberrations in the microglial immune response cause brain damage and accelerate Aβ and tau deposition.

Genetic mutations: Diseases may be caused due to mutations in the genes on chromosomes 1, 14, 19 and 2.

- One connection lies between a gene on chromosome 19, called the Apolipoprotein E gene (especially E4 allele), and late-onset Alzheimer's. That's the most common form of the disease and this allele is also a risk factor for hypercholesterolemia.
- An abnormality of the APP molecule that renders it more amyloidogenic. This appears in infrequent autosomal dominant genetic forms of AD. In these patients, AD develops before age 65 (presenile dementia) due to mutations of the presenilin 1 and 2 genes (PSEN1 and PSEN2) on chromosomes 14 and 1 respectively. The presenilins are catalytic components of γ-secretase.
- The gene for APP is on chromosome 21. Trisomy 21 (Down syndrome) provides a clear mechanism for Aβ deposition. Persons with this condition produce one and a half times as much APP as normal people do and develop AD at a younger age, some of them in their 20s.

Causes of Alzheimer Disease [15,16]

A definite cause is still to find out, however certain risk factors are associated in the occurrence of Alzheimer Disease

Sociodemographic Profile

- **Age:** growing age >65 years.
- **Sex:** women are more at risk (2/3rd cases are women, reason not known).
- **National and ethnic profile:** 58% of all people with dementia live in countries currently classified by the World Bank as low or middle income countries. The proportion of people with dementia living in these same countries is estimated to increase to 63% in 2030 and 68% in 2050.

Familial Predisposition: There may be 3-5-fold increase in risk when a first degree relative such as parents, brother, sister is affected, that is linked to genetic changes on four chromosomes 1, 14, 19, and 21.

Less Cognitive Reserve: less education and less brain activity increase vulnerability to dementia.

Cardio-Vascular Risk Factors: Factors like hypertension, diabetes mellitus, elevated homocysteine, and hypercholesterolemia are also seriously implicated to Alzheimer's disease. Diabetes mellitus: Type 2 diabetes is an important risk factor for AD. AD patients have low levels of insulin and insulin resistance in the brain. These changes impair energy metabolism in neurons and adversely affect signaling pathways dependent on insulin and its receptors. Furthermore, nonenzymatic glycation of proteins produces neurotoxic derivatives that aggravate oxidative damage. Type 3 Diabetes: Scientists now call Alzheimer's disease "Type 3 diabetes." as AD represents a form of diabetes that selectively involves the brain and has molecular and biochemical features that overlap with both type 1 diabetes mellitus and type 2 diabetes mellitus.Homocysteine increases with advancing age and is elevated in persons with polymorphisms of 5,10-Methylene-Tetrahydrofolate Reductase (MTHFR), an important enzyme involved in folate metabolism. Elevated homocysteine and decreased folate are associated with increased free radicals, cytosolic calcium, glutamate excite-toxicity, apoptosis, and decreased levels of ATP.

Predisposition in the Presence of Certain Medical Illness: Depression, Hypothyroidism, Herpes simplex, estrogen replacement therapy.

Diagnosis of AD [17-19]

Importance of Early Diagnosis

Although the onset of Alzheimer's disease cannot yet be stopped or reversed, an early diagnosis is important due to following reasons:

- A better chance of benefiting the patient.
- More time to plan for the future i.e., decisions about financial and legal matters.
- Increased chances of participating in clinical drug trials, helping advance research.

Mainstay of Diagnosis

There is no definite single test, but Alzheimer's could usually be diagnosed through a systematic assessment with a combined effort of Physician-Neurologist-Psychiatrist-Psychologist as follows:

Thorough Medical History for symptoms from the patients & Collateral history from relatives.

A physical and neurological examination to rule out other neurological disorders.

Presence of risk factors.

Neuro-psychometric assessment for scaling cognitive functions.

Smell Test.

Brain imaging- CT, fMRI and PET.

Cerebrospinal Fluid (CSF) assays.

Genetic Testing.

Blood protein assay.

Thorough Medical History for Symptoms from the Patients & Collateral History from Relatives

Memory Loss - Inability to remember new information is hallmark symptom (generally of insidious onset). The slow onset

of memory loss usuallyaccredited to normal ageing and is often identified only in retrospect as the onset of Alzheimer's disease. Symptom like 'difficulty with word finding' is also common with increasing age in everyday life to varying degrees. It is only when the symptoms interfere significantly with social and daily work activities, or are recognised by others. Appearance of symptoms may be as follows:

- Difficulty performing familiar tasks due to weak memory.
- New problems with writing or speaking.
- Confusion with time and place.
- Poor or decreased judgment ability
- Problems with abstract thinking (drawing logical conclusions from a set of observations).
- Misplacing things and losing the ability to retrace steps.
- Trouble understanding visual images and spatial relationships.
- Withdrawing from social activities.
- Changes in mood or behavior (psychiatric symptoms), major depression occurs in 24-32% of cases, anxiety in 17-27%, apathy in up to 41%, and delusions in 23%.

Physical and Neurological Examto Rule out Neurological and Other Disorders

- Cardio-vascular and respiratory system examination,
- Blood Pressure, Heart Rate and body temperature
- Reflexes
- Muscle tone, strength and ability to get up from a chair and walk
- Sense of sight and hearing
- Coordination and Balance

Presence of Risk Factors

By a meticulous history and investigation, presence of any risk factor should be determined.

Neuro-psychometric Assessment

A brief mental status test to assess the memory and other thinking skills can be carried out using the Mini Mental State Examination (MMSE). Neuropsychological testing may provide additional details about mental function compared with those of a similar age and education level and staging (Figure 1).

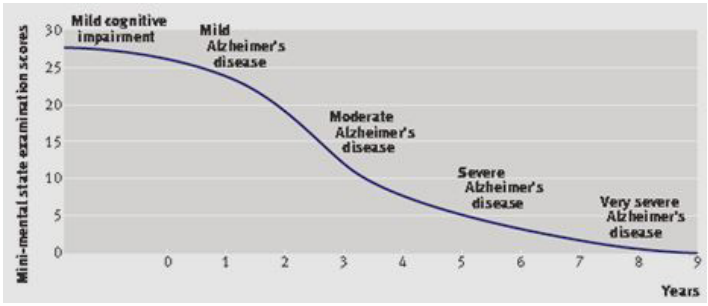

Figure 1: Staging of Alzheimer's Disease according to MMSE scoring.

- Mild cognitive impairment (may or may not be pre-Alzheimer condition): Complaints of memory loss, intact activities of daily living, no evidence of Alzheimer's disease. MMSE score 30-25
- Mild Alzheimer's disease: Forgetfulness, short term memory loss, repetitive questions, hobbies, interests lost, impaired activities of daily living. MMSE score24-15
- Moderate Alzheimer's disease: Progression of cognitive deficits, dysexecutive syndrome, further impaired activities of daily living, transitions in care, emergence of behavioural and psychological symptoms of dementia. MMSE score14-05
- Severe Alzheimer's disease: Agitation, altered sleep patterns, assistance required in dressing, feeding, bathing, established behavioural and psychological symptoms of dementia. MMSE score<5
- Very severe Alzheimer's disease: Bedbound, no speech, incontinent, basic psychomotor skills. MMSE score 0.

Smell Test [20]

It is a known fact that cholinergic neurons of basal forebrain send neural projection to areas of brain involved in cognition as well as smell. Battery of four 'Odour Tests' to measure people's olfactory ability (sense of smell) have been developed:

- First test is called OPID (Odour Percept Identification), here participant is exposed to odours of pineapple, smoke, lemon, soap, grape, leather, strawberry, menthol, lilac, and clove. He has to experience each one for 2 seconds and then had to match the odour with the one of the 10 listed above.
- The second test called OAS (Odour Awareness Scale), involves completing a questionnaire which is assessed in view, if these odours trigger any memories.
- The third test (OPID-20) included more odour testing including garlic, baby powder, cherry, banana, fruit punch, grass,

orange, chocolate, peach, and dirt. The participants are asked if any of the odours matched any from the first test, and to give the best word describing each odour.

- In the final test called OD (Odour Discrimination), participants are tested with two odours and then asked if they are the same or different. This process is repeated 12 times with various paired scents.

OPID-20 especially shows, those participants who would have cognitive impairment also, has difficulty remembering the odours from the first test. This correlates with studies showing that people with dementia/Alzheimer's risk had thinning of the brain, in particular, the hippocampus and entorhinal cortex.

Brain imaging-CT, fMRI, PET Scan using FDG-PET, DTI [21]

- Computerized Tomography (CT): A CT scan produces cross-sectional images (slices) of brain. It's currently used chiefly to rule out tumours, strokes and head injuries.
- PET scan using (^{18}F) Fluorodeoxyglucose (FDG-PET): measures cerebral glucose metabolism and blood flow-these are indicators of synaptic function. In AD, there is decreased metabolism in the temporo-parietal cortex at resting state, reflecting a defect in episodic memory.
- Functional MRI (fMRI) detects change in neuronal activity during the performance of cognitive tasks, by measuring Blood-Oxygen-Level-Dependent (BOLD) signal. In AD, there is decreased activation of the hippocampus during episodic memory tasks.
- Diffusion Tensor Imaging (DTI) detects axon density by measuring diffusivity of water molecules in the white matter. In AD, the white matter connecting to the hippocampus shows decreased density, probably due to neuronal loss.

Cerebrospinal Fluid Examination

In special circumstances such as rapidly progressive dementia or very young onset dementia, a cerebrospinal fluid examination may be performed. The spinal fluid can be tested for biomarkers that indicate the likelihood of Alzheimer's disease. Low CSFAb42, the biomarkers of neuronal degeneration or injury, elevated CSF tau (both total and phosphorylated tau).

Genetic Testing [22,23].

Genetic testing is mainly advocated in early onset familial Alzheimer disease (eFAD) that is regarded as an 'autosomal-dominant genetic disease'. This means that in each family it is caused by a mutation in a single gene, and that a single copy of the mutant gene, is inherited from one parent, can cause the disease. The discovery in the mid-1990s of eFAD genes produced the threat of knowing one's genetic future, not only for patients but also for their children and entire families. DNA testing has been used since the mid-1990s for Huntington Disease (HD) and certain types of cancer but consultations for AD is still less than l but growing.

Blood Protein Assay [24]

Development of blood-based biomarkers is under experimental state since there is the massive dynamic range of proteins in blood especially large amount of albumin and Gamma globulin those mask the presence of less abundant proteins and blood also lacks direct contact with brain. The concentrations of most known possible biomarkers are significantly lower in the blood than reported in CSF. For example, Aβ peptide concentration is 100-fold lower in blood than in CSF.

However, blood based biomarkers like metabolomics and transcriptomic-based markers show hope of being the potential markers of AD especially in view of disruption of blood brain barrier disruption in aging brain causing strengthening of the relationship between blood and brain.

Treatment [25]

The fact is, still there is no definite cure for AD.

The goals of Treatment

Slow the progression of the disease (although this is difficult), Manage symptoms, such as behaviour problems, confusion, and sleep problems, Change the home environment to make daily activities easier, Support family members and other caregivers, Control problems with behaviour.

Pharmacotherapy-Drugs

Current Alzheimer's medications can help for a time with memory symptoms and other cognitive changes. Two types of drugs are currently used to treat cognitive symptoms: One type is Cholinesterase inhibitors:These drugs work by boosting levels of a cell-to-cell communication by providing a neurotransmitter (acetylcholine) that is depleted in the brain in AD those can also improve neuropsychiatric symptoms. Commonly prescribed cholinesterase inhibitors include donepezil:5-10 mg (Aricept), galantamine: 8-24 mg (Razadyne) and rivastigmine: 6-12 mg (Exelon). Second type is Glutamatergic partial antagonist-Memantine:10-20 mg (Namenda):It works by blocking a neurotransmitter called glutamate. Glutamate's job is to excite nerve cells in the brain, but it is seen that in people with Alzheimer's, glutamate actually can cause damage to neurons by blocking glutamate and thereby slowing the progression of the diseases. It is often used in combination with the cholinesterase inhibitors, and also is more effective if it is started in the earlier stages of the disease. For psychiatric or psychological symptoms, sometimes other medications such as antidepressants are used to help control the behavioral symptoms.

Newer Approaches to Treatment

RivastigmineTransdermal Patch

This is used to treat Alzheimer's disease that affects the ability to remember, think clearly, communicate, and perform daily activities and may cause changes in mood and personality. Rivastigmine is in a class of medications called cholinesterase inhibitors. It im-

proves mental function (such as memory and thinking) by increasing the amount of a certain natural substance in the brain.

Insulin Nose Spray [26]

Insulin-a hormone that helps regulate blood sugar- appears to play a role in normal memory processes. Insulin irregularities may contribute to cognitive and brain changes associated with Alzheimer's disease in some new research studies.

Human Vaccine for Alzheimer's Disease [27]

It was reported recently in transgenic mice that over express a mutant APP develop AD neuropathology. Active immunization of young animals with Aβ and passive immunization with Aβ antibodies prevented the development of AD; however, in human, stillvaccine trials are in progress.

Stem Cell Treatment [28].

Like all other forms of dementia, Alzheimer is also caused due to severe nerve cells damage, stem cell therapy has been tried with some hope in future treatment.

Mending Epigenetics [29,30].

Epigenetics is an emerging discipline, for studying the effects of immediate surrounding environment like diet, climate, water, physical activity etc. influence person's biological make up by altering DNA and activity of genes of body cells. Dizygotic (fraternal) and monozygotic (identical) twins show strong evidence of epigenetic impact in humans, for example development of one particular disease in one but not in other. It is likely that epigenetics may ultimately turn out to have a greater role in disease than genetics. Inheritance of paternal environment factors induced traits across generations may also occur through small non-coding RNA signals those are transmitted via the paternal germline. Epigenetic has the potential to explain mechanisms of aging, human development, and the origins of cancer, heart disease, mental disorders, as well as several other conditions. Improving the immediate milieu through life style modification is not exception as a therapy for AD as well.

Use of Biomaterials for the Treatment of AD [31]

The increasing incidences of AD and inadequate effectiveness ofpresent time treatment modalities have paved a newer strategy for biomaterials and their applications. Biomaterials are very useful for the delivery of therapeutic agents, such as drugs, proteins, and/or cells, in order to treat diseases and regenerate tissues. Recently, application of nano-sized delivery systems has increased the usefulness and delivery potential of biomaterials especially to brain region.

Alzheimer's Prevention 'A Holistic approach' [32-34].

Although exact processes to prevent AD are still to find out but some proposals are as follows to lower the risk of this disease.

Diet

Vegetarian diet like whole grains, fruits and vegetables, nuts, olive oil, other healthy fats should be preferred and fish and shellfish may be taken. Consuming red meat is not healthy.Diet regime with antioxidants (vitamin C, vitamin E, beta-carotene) that are present in food like berries (blueberries, strawberries and cranberries) have been shown to improve cognitive function in experimental animals. Curcumin (antioxidant in turmeric) has been shown to suppress building-up of harmful amyloid plaques in the brains of rats.

Mental Activity

Activity in brain and change in routine thinking processes like listening and watching televisionprograms, reading newspapers, playing puzzle games, visiting new places, learn a new language, socializing work as mental boosters to increase the cognitive reserve. Perhaps such activities improve synaptic connections and neuronal networking to form alternative routes to information travelling.

Exercise

Daily aerobic exercise for 30 minutes is very effective step in preventing AD including psychological and behavioral symptoms.

Reducing Cardiovascular Risk Factors

Decreasing the level of homocysteine, quitting smoking, well controlled diabetes mellitus and hypertension are important for good cardiovascular health and indirectly prevent AD. Homocysteine is an amino acid that's a building block of protein and higher than normal concentration is a risk factor for AD. Consumption of folate (romaine lettuce, spinach, asparagus, broccoli, collard greens, parsley, cauliflower, beets, lentils etc) and vitamin B-6 and B-12 (fish, potatoes, non-citrus fruits, fortified cereal, poultry, eggs etc) are simple ways to prevent AD.

G. Caregiver's Role [35]

- Helping with Instrumental Activities of Daily Living (IADLs), such as household chores, shopping, preparing meals, providing transportation, arranging for doctor's appointments, managing finances and legal affairs, and answering the telephone.
- Helping the person take medications correctly, either via reminders or direct administration of medications.
- Helping the person adhere to treatment recommendations for dementia or other medical conditions.
- Assisting with Personal Activities of Daily Living (ADLs), such as bathing, dressing, grooming and feeding and helping the person walk, transfer from bed to chair, use the toilet and manage incontinence.
- Managing behavioral symptoms of the disease such as aggressive behavior, wandering, depressive mood, agitation, anxiety, repetitive activity and night time disturbances.
- Finding and using support services such as support groups and adult day service programs.

- Making arrangements for paid in-home, nursing home or assisted living care.
- Hiring and supervising others who provide care.
- Assuming additional responsibilities that are not necessarily specific tasks.
- Providing overall management of getting through the day.
- Addressing family issues related to caring for a relative with Alzheimer's disease, including communication with other family members about care plans, decision-making and arrangements for respite for the main caregiver.

AD Prognosis [36]

It varies from person to person. If AD develops quickly, it is more likely to worsen quickly. People with AD often die earlier than normal, although a person may live anywhere from 3 to 15 years after diagnosis. The final phase of the disease may last from a few months to several years. During that time, the person may become totally disabled, of erratic behavior and loss of body functions complete dependency on others. Painfully it takes away a person's identity, ability to connect with others, think, eat, talk, walk and find way to home, ultimately vegetative life and death due to infection or organ failure.

Conclusion

We urgently need to find more definitive biomarkers and treatment for Alzheimer Disease! No doubt, in India we need to spread more awareness.

Acknowledgement

My daughter Ms Gauri Mittal for writing a striking poem to express agony of AD patients.

Desolation of Alzheimer patient

The laughter of childhood,

The warmth of a parent's embrace,

Those of lullabies and goodbyes,

All gone into the shade.

Of tears and joys,

Of love and loss,

All memories that made up my life erased.

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