International Journal of Advanced Research in Pharmacy and Education
Volume 2, Issue 1 - 2020, Pg. No. 16-23
Peer Reviewed & Open Access Journal

Review Article

Etiology, Symptoms, Neuropathology and Management of Alzheimer's Disease: A Neurodegenerative Disorder

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How to cite this article:
Vishwakarma VK, Paswan SK, Shukla N et al. Etiology, Symptoms, Neuropathology and Management of Alzheimer's Disease: A Neurodegenerative Disorder. *Int J Adv Res Pharm Edu* 2020; 2(1): 16-23.

Date of Submission: 2020-03-29
Date of Acceptance: 2020-05-06

A B S T R A C T

Alzheimer's disease (AD) is a neurological disorder reflected by memory loss and affecting daily living activities. The pathological alterations of Alzheimer's disease are mainly through neuritic plaques which are the accumulation of beta-amyloid protein and also neurofibrillary tangles. This review has been accomplished on various pathological alterations, causes, treatment and management of Alzheimer's disease targeting towards cholinergic deficiency, inflammation and oxidative stress. The management and therapy of Alzheimer's disease include Memantine, cholinesterase inhibitors, ACE inhibitors, secretase inhibitors and anti-inflammatory drugs including various vitamins, minerals and herbal drugs. This review aims to focus on the mechanism of oxidative stress including its role in the progression of the disease.

Keywords: Alzheimer's Disease, β-amyloid Precursor Protein, Anti-inflammatory Drugs, Acetylcholinesterase Inhibitors, Secretase Inhibitors, N-methyl D-aspartate Receptor Antagonist, Neurofibrillary Tangles

Introduction

Alzheimer's Disease (AD) is a chronic, progressive and irreversible neurodegenerative disorder that induces severe cognitive impairment in elderly individuals. Although, the early stages of AD associate with mild cognitive decline and progressive memory loss, at the late stages patients exhibit personality alteration.[1] Alzheimer's Disease (AD) is indicated by loss of memory and cognition, impairment in performing daily living activities and many behavioural and neuropsychiatric illnesses. With an increase in the geriatric population in India, numbers of AD patients are increasing day by day.[2]

Etiology of AD

The specific reasons for AD are obscure. Nonetheless, most specialists concur that AD, like other normal constant illnesses, creates because of various factors instead of a solitary reason. These factors include a variety of changes in the brain that begin as many as 20 years before the appearance of symptoms. Increasingly, the period between the initial brain changes of AD and the symptoms is considered by scientists to represent the "continuum" of AD. At the start of the continuum, the individual can function normally, despite these brain changes and the individual shows impairment and decline in cognitive function.[3]

Senile Plaques

Senile plaques consist of extracellular deposits of amyloid material and are associated with swollen, altered neuronal processes called dystrophic neurites. Like amyloid, complex sugar polymer components (glycosaminoglycans) are thought to be critical in the assembly of these deposits. The cerebral amyloid is characterized by its major peptide component, β-amyloid, 40-42 amino-acid fragment of the transmembrane protein, β-amyloid precursor protein (β-APP). The way that the thickness of decrepit plaques doesn't increment with age and recommends that cerebrums change from sans plaque to plaque-bearing status in a brief timeframe; the component liable for this change is not characterized.[4]

The Role of Genes

Several point mutations in the gene coding for β-APP on chromosome 21 are sufficient to cause early-onset autosomal dominant familial AD while some mutations increase the production of β-amyloid.

Role of mild inflammation

One hypothesis is that AD may represent a chronic inflammatory disease. The brains of AD patients show evidence of mild inflammation, including microglial and complement activation, and the presence of inflammatory cytokines.[5]

Potential Mechanisms Associated with Aging and AD

Ageing is the major risk factor of AD in the general population. Recent research has identified potential mechanisms related to ageing which may lead to the development of the disease. One thought is that free radicals (reactive oxygen species) produced during cellular respiration play a significant role in the process of ageing and the development of AD. According to another school of thought, the mechanism related to ageing is messenger RNA as mutations in messenger RNA have been reported in older rodents and elderly humans. The deletion of two consecutive bases in a protein result in an altered reading frame and thus, a protein having an amino acid sequence unrelated to that specified in the original gene sequence. The predicted abnormal forms of two proteins relevant to the pathogenesis of Alzheimer.[6]

Symptoms of AD

AD affects people in different ways, but the most common symptom pattern begins with gradually worsening ability to remember new information. The following are warning signs of AD.[7]

- Difficulty in following a daily routine or familiar tasks at home and work due to memory loss
- Inability to plan and solve problems
- Confusion with time or place
- Difficulty in understanding visual images and spatial relationships
- Problem with speaking new words or writing
- Losing the ability to retrace steps and misplacing things
- Changes in mood and personality
- Other symptoms include confusion, poor judgment, language disturbance, withdrawal from work or social activities, and hallucinations
- Occasional seizures, increased muscle tone, myoclonus, Parkinsonian features, incontinence

Cognitive Changes

These changes are characterized by the following sequential stages:

No Impairment

Memory and cognitive abilities appear normal.

Very Mild Cognitive Impairment

Nearly half of the people above 65 years of age face problems related to concentration. They face problem in recalling words. Memory lapses and changes in thinking are rarely detected by family, friends or medical personnel.

Mild Cognitive Impairment

While subtle difficulties begin to impact function, the person may consciously or subconsciously try to cover up his or her problems. Hope to encounter trouble with recovering words, association, arranging, losing objects, and overlooking ongoing realizing, which can influence life at home and work. Depression and other changes in mood can also occur. Duration: 2-7 years.

Moderate Dementia

Issues taking care of accounts result from numerical difficulties. Ongoing occasions and discussions are progressively overlooked, albeit a great many people in this stage despite everything know themselves and their family. Regularly pull back from social circumstances, deny issues and become cautious. The precise determination of AD is conceivable at this stage, keeps going around 2 years.

Early Severe Dementia

In which the patients are no longer in the position to manage independently or unable to recall personal history details and contact information, frequent disorientation regarding a place. People in this stage experience a severe decline in numerical abilities and judgment skills, which can leave to vulnerable scams and only at risk from safety issues. Basic daily living tasks like feeding and dressing require increased supervision. This stage remains for about 1-2 years.

Middle Severe Dementia

There is a lack of awareness about the present events and are unable to accurately remember past incidents. In this stage, there is a further weakening of conveying own day by day living exercises like toileting, dressing, and eating, yet are as yet ready to react to nonverbal improvements, and impart joy and torment through conduct. Agitation and hallucinations often show up in the late afternoon or evening. Peoples in this stage, start to wander around and look at family members with suspicion.

Late Severe Dementia

Is the last stage, where physical activity becomes restricted like the person is not able to walk or sit by himself. The person has to be taken care of at all times, even with the routine work. In the worst case, the patient may lose their capacity to even swallow.[8]

Risk Factors Identifying with AD

The AD is an illness of mature age, however, does not influence all. In most cases, the illness is analyzed at age ≥65years. Most individuals are said to have late-beginning of the AD. If the illness is found in an individual <65years, it is alluded to as the "beginning stage" of AD.[9]

Family History

Individuals who have a family history (parent, brother, or sister) with AD are more likely to develop the disease than those who do not have a first-degree relative with AD. Those who have more than one first-degree relative with AD are at even higher risk of developing the disease. When diseases run in families, heredity, shared environmental factors, or both may play a vital role.[6]

Head Trauma and Brain Injury

Head injury, head trauma, and traumatic brain injury are associated with an increased risk of AD and other dementias. Moderate head injuries are associated with twice the risk of developing AD compared with no head injuries, and severe head injuries are associated with 4.5 times the risk.[10]

Role of Neuropathological Alterations in AD

Pathologically, AD is characterized by intracellular neurofibrillary tangles and extracellular amyloid protein deposits which contribute to senile plaques. In recent years, researches have been conducted in the field of pathogenesis for the examination of novel pharmacological therapeutics which are focused towards the pathophysiological condition of the disease.[11]

Amyloid β-peptide

AD in brains is prevalently portrayed by the presence of two highlights - Senile plaques and neurofibrillary tangles. These plaques, which are thought to assume a focal part in the fiery course, are made basically out of stores of β-amyloid (Aβ) peptide. β-amyloid is a little bit of APP. β-amyloid at first collects and structures the plaques between the neurotransmitters in the cerebrum and upsets cell to cell correspondence. The 39-to 43-buildup Aβ peptide is delivered from the cleavage of APP by β- and γ-secretase. Application is a pervasively communicated huge sort 1 transmembrane protein, the debasement of which enters either the amyloidogenic or the non-amyloidogenic pathway, potentially relying upon in the case of handling happens inside α-lipid pontoons and phospholipid spaces, separately.[12] The more common fate of APP is cleavage by α-secretase, to generate a secreted ectodomain of APP, which acts as a neurotrophic protein, and a C-terminal fragment that is degraded internally. It is suggested that APP processing may be directed to either pathway by modulating the cholesterol content of the membranes. A contribution of transforming growth factor-β1 (TGF-β1) in elevating the expression of β APP by transcriptional and posttranscriptional events, thereby promoting antibody production in astrocytes and possibly enhancing plaque formation. Studies have shown that TGF-β1 induces the overexpression of APP in astrocytes but not in neurons, leading to TGF-β1-induced Aβ generation in both murine and human astrocytes.[13] Interleukin-1 (IL-1) has also been implicated as a driving force for amyloid plaque deposition through increasing APP synthesis in astrocytes. Scientists have been demonstrated in rats that injection of IL-1 into the cerebral cortex results in an increase in APP protein synthesis by astrocytes. Accumulation of Aβ-peptide forms diffuse and non-neuritic plaques. As Aβ-peptide continues to accumulate and APP over-expressing, dystrophic neuritis become associated, the plaques evolve into diffuse and neuritic plaques which condense to form dense core neuritic plaques.[14]

Tau and Formation of Neurofibrillary Tangles

The subsequent major portraying factor for AD is the presence of neurofibrillary tangles. Tangles are involved 95% groups of matched helical fibres made out of the microtubule-related protein tau, alongside 5% of related straight fibres. In sound neurons, the main capacity of tau is to help adjustment of microtubules, the sinewy structures to a great extent answerable for correspondence and transportation inside the cell. Tau proteins found in neurofibrillary tangles, however, are abnormally hyperphosphorylated, making them unable to bind to microtubule assemblies.[15]

Oxidative stress

Oxidative stress is observed in the brain of Alzheimer patients. This increase has been well documented with markers for protein, Deoxyribonucleic acid (DNA), and RNA

oxidation as well as lipid peroxidation.[16]

Protein oxidation

Protein oxidation is indexed in the AD brain by an increase in protein carbonyls, 4-hydroxyl-2-trans-noneal (HNE) and 3-nitrotyrosine (3-NT) modified proteins. Scientists have stated that an increase in protein carbonyls in the hippocampus and parietal cortex, but not in the cerebellum, where there is less significant AD pathology.[17]

Lipid peroxidation

Intensified lipid peroxidation has been seen in AD. Examination of AD cerebrums exhibits an expansion in free HNE in the amygdala, hippocampus, and parahippocampal gyrus of the AD mind contrasted and age-coordinated controls. A noteworthy rise of free HNE in ventricular cerebrospinal liquid and serum gives a potential biomarker to AD. Protein-bound HNE causes conformational changes and at last modifying the capacity of proteins. Hence, measures identified with excitotoxicity might be encouraged, while measures identified with the expulsion of HNE from neurons might be undermined.[18]

DNA oxidation

DNA is the primary target of Reactive Oxygen Species (ROS), leading to cellular ageing. Due to the high oxygen consumption rate by the brain, ROS may contribute to neuronal damage in ageing and neurological disorders. Oxidative damage to DNA by ROS results in strand breaks, DNA-DNA and DNA-protein cross-linking, and sister-chromatid exchange and translocation. DNA bases are also attacked by the lipid peroxidation products HNE and acrolein, which leads to the formation of bulky exocyclic adducts. This modification can cause inappropriate base pairing that forms an altered protein. DNA oxidation by ROS also produces oxidized base adducts, such as 8-Oxo-2'-deoxyguanosine (8-OHdG). Guanine, since it has the least oxidation capability of the four DNA bases, is the most promptly oxidized base and, in this way, the most generally utilized investigation of DNA oxidation. Previous studies have demonstrated an increase in DNA strand breaks in the diseased brain, which results in depletion of energy stores and cell death.

RNA Oxidation

Studies have been shown that 30-70% oxidation of the mRNAs in the frontal cortex of the AD brain occur in comparison to only 2% oxidation in normal individuals. Increased levels of 8-Hydroxyguanosine (8-OHG) have also been reported in the hippocampus and the cerebral neocortex of the AD brain, whereas the 8-OHG level in the cerebellum was not significantly altered compared with controls. An increase in 8-OHdG has been identified not only in brain tissue but also in CSF from AD patients. RNA oxidation in the diseased brain could render the cell incapable of initiating the protein synthesis, hindering the cell defence against further oxidative damage, an effect observed in AD [20].

Mitochondrial dysfunction

Mitochondrial dysfunction in the diseased individual is central to the development of oxidative stress because it is a primary source of cellular oxidants. Positron emission tomography has provided specific evidence of brain metabolic abnormalities associated with the disease, which precede neuropsychological impairment and visual atrophy.[21]

ROS and Glutathione System

ROS, such as superoxide, hydroxyl radicals and hydrogen peroxide, and RNS such as nitric oxide and nitrogen dioxide, are generated normally during oxygen intake, the oxidative metabolism of some substances and after the consequences of infection. Cells maintain the balance between the production of ROS and reactive nitrogen species (RNS) and their detoxification via effective enzymatic and non-enzymatic antioxidant systems. The glutathione system, which consists of glutathione, glutathione peroxidase, and glutathione reductase, and the thioredoxin system, consisting of thioredoxin and thioredoxin reductase, are two important enzyme systems involved in maintaining homeostasis. Catalase and superoxide dismutase are two other significant antioxidant enzymes naturally produced by the body. [22, 23] Oxidative pressure causes oxidation of biomolecules creating an overproduction of free radicals that can harm cells. The reasonable instances of oxidative harm are changed protein and catalyst work, because of tertiary structure alteration, the decimation of basic proteins, transformations in DNA, and oxidation of layer lipids promoting film brokenness and cell lysis.[24]

In AD patients, the oxidative burst is an important source of oxidative stress in the inflammatory conditions.

Treatment

Interdisciplinary methodologies consolidating organic chemistry, sub-atomic science, and transgenic demonstrating have uncovered some sub-atomic systems of AD. Novel developments in the field of chemistry, radiology, and systems biology are beginning to provide useful biomarkers, and the emergence of personalized medicine is assured to transform pharmaceutical development and clinical trials.[25]

Currently available treatments i.e. acetylcholinesterase inhibitors (Rivastigmine, Galantamine, Donepezil) and N-methyl d-aspartate receptor antagonist (Memantine) contribute minimal impact on this disease and target late aspects of the disease. These drugs reduce the progression of the disease, provide symptomatic relief but fail to achieve

a certain treatment. While the neuropathological features of Alzheimer's disease are recognized but the details of the mechanism could not be achieved. This absence of accessibility of information concerning the pathogenic cycle might be the conceivable purpose behind the non-accessibility of compelling treatment which can forestall beginning and movement of the infection.[11]

AD is regarded as brain amyloidosis. Deletion of amyloid beta-protein deposition is one of the most favourable targets for the treatment. A cascade of pathophysiological events is triggered in Alzheimer. There is a prominent loss of cholinergic, noradrenergic, dopaminergic, and GABAergic neurons transmission in AD. Neurotransmitter based treatments with cholinesterase inhibitors (ChEIs) and N-methyl- D-aspartate (NMDA) receptor antagonists are now a day in use.[26]

Anticholinesterase inhibitors

Symptomatic treatment of AD is based on the enhancement of cholinergic activity by inhibiting acetylcholinesterase enzyme. This methodology is upheld by three arrangements of realities: Brain biopsies and post-mortem examination considers have demonstrated that patients with AD have decreased cortical action of choline acetyltransferase ChAT, the compound that blends ACh from choline. Additional post mortem studies have shown a pattern of cholinergic denervation with a reduction in presynaptic muscarinic type 1 and nicotinic receptors, with relative preservation of postsynaptic muscarinic type 2 receptors. The loss of cholinergic neurons in the nucleus basalis of Meynert and other subcortical nuclei from which originate diffuse cortical projections support this hypothesis. These drugs act by slowing the biochemical breakdown of acetylcholine and thereby, facilitates cholinergic neurotransmission. Rivastigmine inhibits both Acetylcholinesterase and Butyrylcholinesterase from degrading ACh. ChEIs are indicated in patients with mild to moderate AD.[27]

NMDA Receptor Antagonist (Memantine)

Overstimulation of the NMDA receptor by glutamate is supported to be a cause in neurodegenerative disorders. Glutamate is the principal excitatory neurotransmitter in the brain. Glutamatergic overstimulation may bring about neuronal harm, which named as excitotoxicity. Such excitotoxicity prompts neuronal calcium over-burden and has been embroiled in neurodegenerative issues. Glutamate animates various postsynaptic receptors, including the NMDA receptor, which has been especially connected with memory cycles, dementia, and the pathogenesis of AD.

Memantine is a generally new medication uniquely produced for use in moderate to serious dementia. Memantine's component of activity is a voltage-reliant, low-moderate fondness, uncompetitive NMDA receptor threat with fast blocking/unblocking energy. Memantine blocks the impacts of unusual glutamate action that may prompt neuronal cell demise and intellectual brokenness. The quick on/off energy and low-moderate liking is the way to Memantine activity since it obstructs the impacts of exorbitant glutamate while safeguarding physiologic enactment of NMDA receptors required for learning and memory. Like other NMDA receptor enemies, Memantine at high focuses can repress components of synaptic versatility that are accepted to underlie learning and memory. In any case, at lower, clinically significant fixations memantine can advance synaptic pliancy and save or improve memory in creature models of Alzheimer.[28]

Angiotensin-converting Enzyme (ACE) Inhibitors

It has been seen that Angiotensin-changing over catalyst (ACE) inhibitors diminish irritation and mental decrease in AD patients by half. Mellow to direct AD subjects with hypertension had less intellectual decrease when given an ACE inhibitor that crosses the blood-mind obstruction (Perindopril or Captopril) than that which doesn't ACE inhibitor that didn't (Enalapril or Imidapril) or a calcium channel blocker (Nifedipine or Nilvadipine). An ongoing report affirmed that the ACE inhibitor moderates the movement of AD. A possible drawback of ACE inhibitors is that they may hinder ACE structure changing over βA 1-42 to less harming βA 1-40, consequently lessening its defensive capacity.[29]

The possible mechanism of ACE inhibitors is that induce reducing angiotensin II (a substance that interferes with memory function by reducing Ach), increasing an enzyme that breaks down βA, and increasing acetylcholine. Another possibility is that angiotensin II is converted to angiotensin III and then to angiotensin IV. Angiotensin IV binds at AT_4 receptor sites, which are most prevalent in the neocortex, hippocampus, and other areas important in cognition and memory. Counteracts a dysfunctional cholinergic system, resulting in more Ach and improved learning and memory.[29]

Nonsteroidal anti-inflammatory drugs

Most researches on nonsteroidal anti-inflammatory drugs have focused on prevention rather than treatment of AD. Animal models have demonstrated that anti-inflammatory cyclooxygenase-2 (COX-2) inhibitors (Rofecoxib) reduced oxidative stress but nonspecific COX inhibitors (Flurbiprofen and Ibuprofen) did not. An animal model revealed that Naproxen, and a MF-tricyclic [3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2(5H)-furanone], COX-2 inhibitors restore memory, but only MF-tricyclic blocked the suppressive effect of βA on synaptic plasticity.[30]

Secretases Inhibitors

β-Secretase inhibitors have been shown to reduce βA in animal models and may have fewer adverse effects.[31]

Brain-derived Neurotrophic Factor

A significant issue is that the BDNF atom is too huge to even think about penetrating the blood-mind hindrance. Human preliminaries, generally examining Parkinson's ailment, have utilized a micropump to straightforwardly implant BDNF into the mind through a cannula embedded into the skull. This is a risky procedure to present for human trials. Also, too large a close can produce serious side effects. Although *in vitro* and animal data are promising, it is unlikely that BDNF therapy will be ever of use shortly. However, physical exercise and diets rich in omega-3 fatty acids have been found to normalize BDNF concentration.[32]

Herbal Treatment and Supplements

Polyphenols

Polyphenols are a group of plant-derived chemical substances with more than one phenol unit. It is claimed that they protect plants from stress induced by ultraviolet radiation, disease, pests, and physical damage. Polyphenols also protect animals by activating several intracellular processes that preserve neurons.[33]

Curcumin

Curcumin is extracted from the plant *Curcuma longa* (turmeric). Turmeric is also used as a spice and common therapy in India, which are our nucleus of ailment to explain why India has a much lower incidence of AD than the United States. Bioavailability may not be a problem for Indians because it is combined with oil in cooking.[34]

Panax

The active components in ginseng known as *Panax ginseng* are thought to be steroid-like compounds called ginsenosides. Ginsenoside Rg3 reduced βA 1-42 by 84% *in vitro* and by 31% *in vivo.*[35]

Ashwagandha

It has been utilized in India for a large number of years to treat various sicknesses. An ongoing audit specified numerous neuroprotective properties of *Withania somnifera*, known as Ashwagandha including mitigating, cancer prevention agent, hindrance of βA, restraint of calcium, hindrance of AChE, and decrease in cell demise. In vitro research has shown that Ashwagandha recovers harmed axons, dendrites, and neural connections. Oral organization of Ashwagandha in the mice turned around harm to the hippocampus and cortex by diminishing neurite decay, reestablishing neurotransmitters, and improving memory.[36]

Nutrients and Hormones

Alpha-lipoic acid

Alpha-lipoic acid (ALA), a fatty acid found in all cells and some foods, is manufactured in the body. The potential mechanisms underlying these and other neuroprotective effects are not written in this review.

Omega-3 fatty acids

Omega-3 fatty acids have many beneficial effects that make who coupled to investigative prospects for AD.

Vitamin B12 and folate

Low levels of vitamin B 12 and folate appear to be associated with an increased rate of cognitive decline. Since AD patients typically have high levels of homocysteine, researchers have examined the possibility that lowering homocysteine would be therapeutic. A combination of vitamins B 12 and B 6 and folate lowered homocysteine both in normal seniors and in those with mild to moderate AD but did not affect cognition. Homocysteine levels appear to correlate with ageing but not with cognition.[37]

Vitamin A

As Vitamin A has been formed that is essential for learning, memory, and cognition, and therefore, vitamin A might have some effect in managing AD. Vitamin A levels in the brain decline with age and are lower still in individuals with AD. Studies have shown that a metabolic product of vitamin A, retinoic acid, is known to slow cell death and offer protection from βA.[38]

Multiple nutrients

Since AD patients often have multiple deficiencies; it makes sense to use multiple supplements. A mixture of acetyl-L-carnitine, aALA mice upon DHA, glycerophosphocholine and phosphatidylserine prevented cognitive decline in aged mice.

Lithium

Lithium is a normally happening mineral found in limited quantities in numerous nourishments. The lithium salts, orotate and aspartate, are now and then suggested for neurogenerative issues.

Lithium builds the degree of a neuroprotective protein called Bcl-2 in the rodent hippocampus and frontal cortex and represses GSK-3, which is embroiled in expanding levels of phosphorylated tau and is believed to be a factor prompting βA plaques and cell passing.[37]

Melatonin

Melatonin is a naturally occurring hormone that is produced in decreasing amounts with age. Melatonin has powerful antioxidant properties. Melatonin readily crosses the blood-brain barrier and enters all cell structures. Despite numerous studies, have been carried out to effect on AD but results were not the substance of poor quality. Since melatonin improves sleep, it might help memory by facilitating memory consolidation.[39]

Conclusion

Although evidence has been presented to suggest that Aβ is central to the pathogenesis of AD, there are many complex secondary events that all determine the outcome of this dreaded disease. Enormous progress has been made in developing strategies to treat AD. Some of these methods include anti-inflammatory, secretase inhibitor anticholinergic, anti-amyloid, antihypertensive, and some natural nutrients, immune and hormones therapy. Currently, the Food and Drug Administration has approved several drugs to treat AD symptomatically but do not provide long-lasting relief from dementia. However, these drugs are frequently associated with adverse drug effects and do not cure the disease by altering their pathology.

In this review, authors have discussed the different aspects of pathological alterations behind Alzheimer's disease and its management through drug therapy and also includes investigational therapeutic strategies relating safety and efficacy. The review will be fruitful for researchers engaged in the experimental research design and novel strategies to treat Alzheimer's disease.

Impact of Alzheimer's Disease on Families

A research study has been emphasized on the personal and social consequences of AD, which appears to go through six and more stages in the progress of the disease. AD also has a drastic effect on family members who serve as caregivers for people with the disease. The burdens and, in some cases, the benefits of the caregiver role differ from person to person.

Race and ethnicity are among the variables that seem to play a role in the caregiver's response.

As Alzheimer's disease progresses, the family may find the changing roles tough to accept. It may lead to some confusion about how to act.

It sometimes takes a while to figure out just who will do what. The family member with dementia usually becomes the family's centre of attention. It is important to remember that different people react to the same situation in different ways.

Acknowledgement

Authors are thankful to the management of All India Institute of Medical Sciences (AIIMS), New Delhi for providing necessary library and Internet facilities for completion of this review.

Conflict of Interest: None

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