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ALZHEIMER AND MODELS - AN AGE BASED REVIEW, DEVELOPMENT OF ALZHEIMER'S AT EARLY AGE AND OLD AGE

Kavitha S. K.*[1], Shilpashree A. T.[2], Nagaraj N. Durgadasheemi[3] and Deepika Pardhe[4]

[1]Department of Pharmacology, R R College of Pharmacy.
[2]Department of Pharmaceutical Chemistry. R. R. College of Pharmacy.

***Corresponding Author: Kavitha S. K.**
Department of Pharmacology, R R College of Pharmacy.

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ABSTRACT
The most highly destructive brain disorder in elderly people is Alzheimer's disease and it has become a major public health problem. It is mainly characterized by an aging process, whereas a steadily increasing effort directed at discovering the etiology of the disease and developing pharmacological treatment. By using symptomatic treatment mainly focusing on cholinergic therapy. Alzheimer disease drugs like glutamine, memantine, ambenonium used for treatment of cognitive disturbance. Alzheimer disease includes anti-inflammatory agents, and antioxidants is characteristic needs for further studies. Antidepressant, antipsychotics, mood stabilizers, anxiolytics, & hypnotics these are also used for the treatment of behavioral and cognitive disturbance. In recent clinical diagnostic guidelines, it shows that the improved treatment for both Biochemical & behavioral problems. In the disturbance for cognitive, randomized, double-blind, placebo-controlled, parallel-group these studies are also used for measuring a performance-based test of cognitive function,in the daily activities of living and behavior cholinesterase inhibitors. Alzheimer's disease is one of the most highly destructive brain disorders of elderly humans. It is a preserved,and disease that is instead becoming a major public health problem. The last nonetheless characterized by an ageing processa steadily increasing effort directed at discovering the etiology of the disease and developing pharmacological treatment. Recent developments include improved clinical diagnostic guidelines and improved treatment of both cognitive disturbance and behavioral & Biochemical problems. Symptomatic treatment mainly focusing on cholinergic therapy has been clinically evaluated by randomized, double-blind, placebo-controlled, parallel-group studies measuring performance-based tests of cognitive function, activities of daily living, and behavior Cholinesterase inhibitors, including galantamine memantine, ambenonium are the recommended treatment of cognitive disturbance in patients with Alzheimer's disease. The role of estrogen replacement, anti-inflammatory agents, and antioxidants is controversial and needs further study. Antidepressants, antipsychotics, mood stabilizers, anxiolytics, and hypnotics are used for the treatment of behavioral disturbance Future directions in the research and treatment of patients with Alzheimer's disease include: applying functional brain imaging techniques in early diagnosis and evaluation of treatment efficacy; development of new classes of medications working on different neurotransmitter systems (cholinergic, glutamatergic, etc.), both for the treatment of the cognitive deficit and the treatment of the behavioral disturbances; and developing preventive methods (amyloid p-peptide immunizations and inhibitors of β-secret's and γ-secretase).

KEYWORDS: Neuropsychology, Cognition, Neuroscience, Mild cognitive impairment, Biomarkers, Clinical trials.

INTRODUCTION
The world population in the aged people with dementia is grown from 35million today and approximately it's about 65million by the year 2030.It observed that in the united states alone, 5 million and 1in 9 ,65 age people. In Alzheimer disease is the most common cause of dementia. According to the centers for disease control & prevention (2009-2012 estimates).[1] The primary physicians and specialists will encounter older adults with dementia a frequently increasing during their careers. In the dementia carries implications for patients, and their families & society it is one imperative for well-rounded physicians to have understanding of this topic. The brief introduction of AD it related to the concept Mild cognitive impairment (MCI) is the stage between the expected cognitive decline of normal aging and the more serious decline of dementia. It can involve problems with memory, language, thinking and judgment that are greater than normal age-related changes.

MCI can present with a variety of symptoms, but is divided generally into two types.

Amnestic MCI -(aMCI) is mild cognitive impairment with memory loss as the predominant symptom; aMCI is frequently seen as a prodromal stage of Alzheimer's disease. Studies suggest that these individuals tend to progress to probable Alzheimer's disease at a rate of approximately 10% to 15% per year.

Nonamnestic MCI -(naMCI) is mild cognitive impairment in which impairments in domains other than memory (for example, language, visuospatial, executive) are more prominent. It may be further divided as nonamnestic single- or multiple-domain MCI and these individuals are believed to be more likely to convert to other dementias (for example, dementia with Lowy body.Its understood from review article.[1] It is on emergency health issue & there are many ongoing highlight effects are carrying out to develop novel therapies from ancient Ayurveda to recent biomarker therapy & and the people who suppressed from dementia are notice to be the age of 40 to 60 this is the age where a person who effects there carrier and settled down in their professional &personal life and this Alzheimer effects both scenario which leads to depression ,antipsychotics, anxiety, sedative after this they start losing progressive and cognitive& functional disabilities leads inflammation. 50 million people in the worldwide its affects AD.With numbers projected to reach 135.5 million by 2050; associated costs for the United States are trillion.[2] In the year of 2013 Dementia Summit, G8 ministers committed to identifying a cure or disease-modifying therapy by 2025,[2] There is no therapy has been for progressive of cognitive and functional disability. Treatment of directed at preventing buildup of β-amyloid (Aβ) or tau has stimulated investigation of alternative including targeting inflammation, immune-related and inflammatory genes with associated of AD which includes myeloid-specific sialic acid binding receptor (*CD33*), triggering receptor expressed on myeloid cell 2 (*TREM2*), complement receptor 1 (*CR1*), and bridging integrator 1 (*BIN1*).[3] Microglial activation is increased in AD. The proinflammatory agent in AD,[4-5] and microglial surface receptors are also Aβ receptors.[6] In early AD, microglia clear Aβ by phagocytosis and produce Aβ-degrading enzymes.[7] However, as AD progresses, accumulation of Aβ stimulates microglial production of proinflammatory agents that are associated with neurodegeneration.[7] The AD.[8,9] of clinical trials data on repositioned drugs identified minocycline hydrochloride among the high-priority drugs to progress on based of Two systematic reviews, based on expert opinion and tolerability, brain penetration, and preclinical and early phase of[9] Minocycline is an anti-inflammatory tetracycline that crosses the blood-brain barrier and inhibits pro inflammatory microglia. In vitro, minocycline protects against Aβ-induced cell death and prevents fibrillization of Aβ.[10] In transgenic mice, minocycline prevents Aβ deposition and neuronal death;[11] reduces tau phosphorylation and insoluble tau aggregates[12] the nitric oxide synthesize, cyclooxygenase-2, down regulates inducible and Aβ precursor protein cleaving enzyme-[13] Minocycline reduces interleukin and tumor necrosis factor levels in mice[14-15] and neuronal death and learning deficits in rats after Aβ administration.[16] We investigated whether minocycline slows the decline in cognitive and functional ability in people with mild AD over a 2-year treatment period and whether giving minocycline hydrochloride at a higher (400-mg) dose than the 200 mg used in standard practice enhanced efficacy.

Classification

Once the PET-based features were extracted from the set of selected ROIs located in both cortical and subcortical regions, feature vectors containing mean-centered voxel intensities were created combining each of the 10 ROIs and assembled for all cases. Supervised classification was performed using four different multiclass methods, which included,

1. linear SVM on raw voxel intensities,
2. RBF kernel SVM on raw voxel intensities,
3. SVM trained with features extracted using principal component analysis (PCA), and
4. random forests (RF) classifier.

Hyperparameters of the RBF kernel were obtained using an exhaustive search grid (described in Section 3), where the parameters were selected based on the maximum in-sample validation accuracy which outperformed polynomial kernels. The tuned hyperparameters were then used to predict the out-of-sample accuracy values on the test set.[17]

Pathophysiology of ad

Neuronal loss and/or pathology may be seen particularly in the hippocampus, amygdala, entorhinal cortex and the cortical association areas of the frontal, temporal and parietal cortices, but also with subcortical nuclei such as the serotonergic dorsal raphe, noradrenergic locus coeruleus, and the cholinergic basal nucleus. 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.[18]

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 fibers 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.[19] Summary of pathophysiology of AD are

shown in Figure 1.

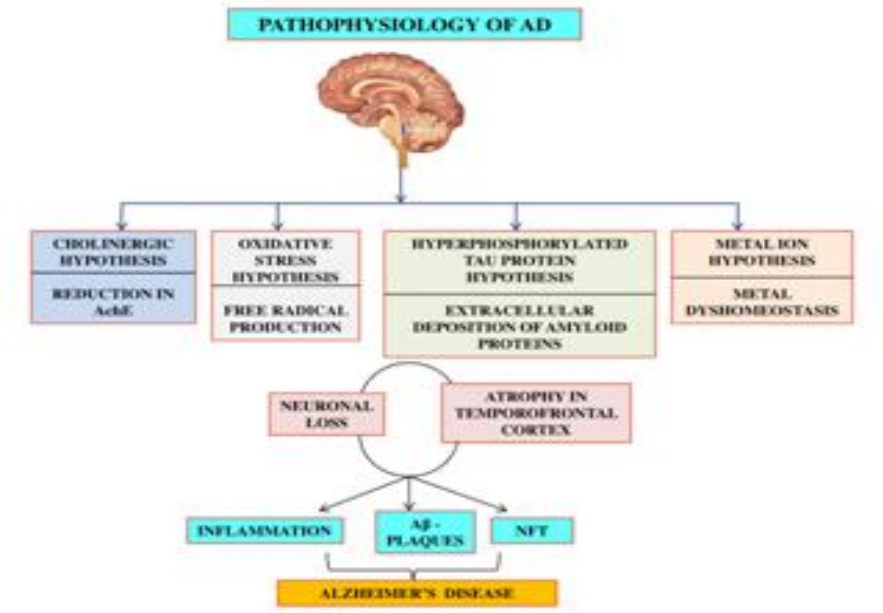

Figure 1. Hypothesis for pathophysiology of Alzheimer's disease.

Hyperphosphorylated tau protein and amyloid β hypothesis

One of the main pathological features of AD is the formation of senile plaques (SP), which is caused by amyloid beta (Aβ) deposition. Normally, Aβ are soluble small peptides, which are produced by the splitting of the precursor protein of amyloid (APP) by the action of α-secretase, β-secretase and γ-secretase. The imbalance between β-amyloid (Aβ) production and clearance leads to various types of toxic oligomeric, namely protofibrils, fibrils and plaques depending upon the extent of oligomerization. The reason of the formation of Aβ is still unclear, but the sequence, concentration and conditions of stability of Aβ are important factors.[20] The pathophysiology of Alzheimer's disease is credited to a number of factors such as the cholinergic dysfunction, amyloid/tau toxicity and oxidative stress/mitochondrial dysfunctions.[21]

Oxidative stress hypothesis

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced in many normal and abnormal processes in humans, they play dual role as both have beneficial functions in cellular signaling pathways and venomous processes that can lead to damage of cellular structures (including cell membrane, lipid, protein, and DNA). The high oxygen consumption of the brain, which utilizes 20% more oxygen than other mitochondrial respiratory tissues, means that the brain is more vulnerable to oxidative stress. The neuron is the basic functional unit of the brain, which contains a large number of polyunsaturated fatty acids. It can interact with ROS, leading to the lipid peroxidation reaction and molecular apoptosis, in addition, less glutathione in neurons is also one of the causes of oxidative stress injury.[20]

Metal ion hypothesis

Metal dyshomeostasis is involved in the progression and pathogenesis of diseases, including neurodegerative diseases and cancer. Ionosphere and metal chelators are well known modulators of transition metal homeostasis, and a number of these molecules are used in clinical trials. Metal-binding compounds are not the only drugs capable of targeting transition metal homeostasis.[22] Current evidence indicates changes in the equilibrium of redox transition metals; mainly copper (Cu), iron (Fe) and other trace metals. Their levels in the brain are found to be high in AD. In other neurodegenerative disorders, Cu, manganese, aluminum and zinc are involved.[23]

Cholinergic hypothesis

The effects of apo-lipo-protein E (APOE) genotype on the useful effect of acetyl-cholinesterase inhibitors (AChEIs) in patients with Alzheimer's disease. AchEI medications are the core of the treatment of AD, and APOE genotype is the most important factor associated with AD. This lack of major effect of APOE is analyzed with respect to the "Cholinergic Hypothesis" of AD, dating from 1976, through the recognition that cholinergic neurons are not the main target of AD. Cholinergic receptor binding is reduced in specific brain regions with mild to moderate AD and is related to neuropsychiatric symptoms. Among healthy older adults, lower receptor binding may be associated with slower processing speed. Cholinergic receptor binding in vivo may reveal links to other key brain changes associated with aging and AD and may provide a potential molecular treatment target.[24] Clinical decrease is related

to an extensive loss of cholinergic neurons formed in the forebrain nuclei (medial) and a related decline in acetylcholine-mediated neurotransmission, drugs tending to regularize acetylcholine transmitter level, such as cholinesterase inhibitors (ChEIs) and donepezil, have for over 20 years served as the foundation of symptomatic therapy for AD.[25]

Clinical criteria

The diagnostic criteria of Alzheimer's disease is based on the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria, according to this the diagnosis is categorized as definite (clinical diagnosis with histological confirmation), probable (typical clinical syndrome without histological confirmation), or possible (atypical clinical features but no alternative diagnosis apparent; no histological confirmation.[26] The recent guiding principle elaborates the concept of Alzheimer's dementia beyond memory loss as its primary symptom and incorporates the possibility that a decrease in other aspects of cognition, such as anomia and impaired executive functioning may be the primary symptoms to be identified. Biomarkers may be used to increase the specificity of diagnosis.[27] Clinicians used the term AD to refer to a clinical dementia entity that basically presents with a specific progressive amnesic disorder following the appearance of other cognitive and neuropsychiatric changes that impair social function and activities of daily living. In the NINCDS-ADRDA criteria, biological investigation (blood and cerebrospinal fluid [CSF]) and neuro imaging examination (computed tomography [CT] scan or magnetic resonance [MR] imaging) were only proposed to exclude other causes of the dementia syndrome (example- vascular lesions, tumors, infectious or inflammatory processes). Typical sensitivity and specificity values for the diagnosis of probable AD with the use of NINCDS-ADRDA criteria are 81% and 73% respectively.[26] Many therapeutic approaches are used to get better the cholinergic neurotransmission, but their function in the pathogenesis of AD is still mystified. Although, enhance in tau protein focus in CSF is described in AD, but many issues remain ambiguous. Accurate and extensive analysis of CSF could be useful to describe the existence of tau proteins in physiological conditions, or released during the development of neurodegenerative disease. The amyloid cascade theory postulates that the neurodegeneration in AD caused by the abnormal accretion of amyloid beta (Aβ) plaques in many areas of the brain.[28] Plasma concentrations of free Aβ could not predict the development of clinical AD, and Aβ concentrations did not change in the years preceding AD diagnosis.[29]

Pharmacology of alzheimer

Acetylcholinesterase inhibitors (AChEI)

The cholinergic hypothesis of AD was put forward following the observation that cognitive deterioration results from a progressive loss of cholinergic neurones and a decrease in levels of acetylcholine in the brain.[30] Thus the mainstay of treatment for AD to date has been the use of agents that inhibit the degradation of acetylcholine within the synapse and so enhance cholinergic neurotransmission. Tacrine was the first AChEI to be approved for the treatment of mild-tomoderate AD over 15 years ago. However, it is no longer prescribed because of its poor tolerability and risk of hepatotoxicity.[31] In the UK, there are three second-generation AChEIs licensed for the treatment of mild-to-moderate dementia in AD: donepezil, rivastigmine and galantamine. These agents differ in their pharmacological actions, particularly in relation to enzyme specificity. Donepezil selectively inhibits AChE, rivastigmine inhibits both AChE and butyr ylcholinesterase (BuChE) and galantamine selectively inhibits AChE but also has activity as an allosteric modulator of nicotinic acetylcholine receptors (nAChRs).[32] Because a decrease in the expression and activity of nicotinic acetylcholine receptors largely contributes to the overall reduction in central cholinergic neurotransmission, this last mechanism is also considered important in the treatment of AD.[33] Memantine Memantine is licensed in the UK for AD but, unlike the AChEIs, it is licensed in moderately severe to severe disease. It has a separate mode of action, acting as an antagonist at N-methyl-D-aspartate (NMDA) receptors, an action believed to be neuroprotective and disease-modifying.[34] Excitotoxicity occurs when there is excessive exposure to the neurotransmitter glutamate or overstimulation of glutamate receptors, resulting in injury or death of neurones. This neuronal death is partly mediated by overactivation of NMDA-type glutamate receptors resulting in an excessive influx of calcium ions (Ca2+) through the receptors' associated ion channel. However, because physiological NMDA receptor activity is essential for normal neuronal function, the total block of NMDA receptor activity would be clinically unacceptable. However, the adamantine derivative, memantine selectively blocks excessive NMDA receptor activity without disrupting normal activity.[35]

Evidence base supporting pharmacotherapy Alzheimer's disease

In recent years, the use of AChEIs has generated much controversy among scientists, consumers and non-statutory organizations. The debate is not over efficacy, since there is reasonable evidence for this, but rather about the magnitude of the benefit. Discussions also continue over whatstage of the disease these agents should be withdrawn. The National Institute for Health and Care Excellence (NICE) recommends treatment with AChEIs for mild-to-moderate AD. Memantine is recommended for severe AD or for moderate AD in people who are either intolerant of, or have a contraindication to AChEIs. NICE also specify that carers' views on a patient's condition should be sought at baseline and follow-up, and that patients who continue on the drug should be reviewed regularly using

cognitive, global, functional and behavioural assessment. NICE defines severity of AD using Mini-Mental State Examination (MMSE) – mild (defined as MMSE 21-26), moderate (MMSE 10-20) and severe (MMSE).

Other dementias

At present, AChEIs and memantine have not been approved for use in non-Alzheimer's dementias. NICE does not recommend their use in vascular dementia (however, AChEIs can be considered in patients with DLB who have non-cognitive symptoms – see below). Cochrane reviews found that the evidence for AChEIs in vascular dementia was inconsistent and, although a meta-analysis of RCTs showed small benefits on cognition with AChEIs and memantine, these improvements were of uncertain clinical significance. There is currently insufficient evidence to support the use of these agents in vascular dementia.[36]

Behavioural and psychological symptoms of dementia (BPSD)

AChEIs may provide some benefit in the management of BPSD; however, their effect is only apparent after several weeks of treatment and trial evidence remains somewhat inconsistent. Similarly, although memantine continues to garner evidence for use in BPSD, its use is still controversial.[36] Future treatments for dementia the future of AD treatment is in disease modification, with the hope and expectation that this will translate into meaningful and significant clinical outcomes. Recently, several investigational drugs for the treatment of AD have failed in early clinical trials, either due to lack of efficacy or concerns over safety. Among these are two anti-amyloid monoclonal antibodies (solanezumab and bapineuzumab) and one γ- secretase inhibitor (semagacestat). These failures have raised the question as to whether patients recruited for inclusion in these trials had AD that was too far advanced to be helped by inhibiting further production or removal of existing β-amyloid plaques. It seems that the only way to tackle this issue is to recruit younger patients who have not yet developed AD, although this understandably raises ethical issues.[37]

Mechanism of alzheimer

Cell types affected by AD include:locus ceruleus, the nuclei of the brain stem (eg raphe nucleus), reticular formation, amygdala, substantia nigra,striatum, hypothalamus. thalamus and claustrum and select regions of the cerebral cortex. The meuronal types affected vary by region according to the expression of neurotransmitters, neuromodulators, neuropeptides.The degenerative process results in cerebral atrophy and neuron loss[38] Disease pathobiology affects non-neuronal cells as well; oligodendroglia, astrocytes, blood vessels, microglia, and the choroid plexus all undergo degenerative processes. Transgenic mouse models of AD indicated that amypoid plaques occur in the vicinity of structural changes capable of altering brain function, including neurite dystrophy and spine loss.[39] Synaptic loss strongly correlates with cognitive deficits in AD. Synapse loss is likely a morphological reflection of the synaptic dysfunction that begins early in disease.[40] Early structural studies of postmortem brain tissues demonstrated that AD patients exhibited a reduced number of dendritic spines and reduced synapse density in the hippocampus and cortex relative to age-matched control brain tissues. There was a direct cor-relation between increased dendritic spine loss and worsening mental status. The progressive atrophy of dendritic spines is therefore proportional to AD pathogenesis and may represent accurate indicator of advancing disease.[41]

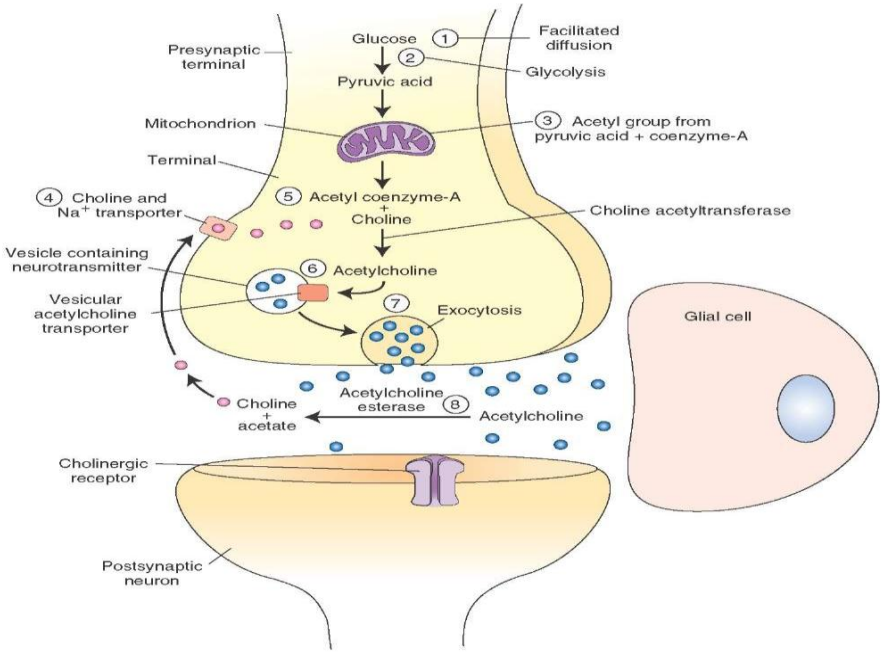

Fig: Mechanism of Alzheimer.

Symptom of alzheimer's disease

The symptoms of Alzheimer's disease progress slowly over several years. Sometimes these symptoms are confused with other conditions and may initially be put down to old age. The rate at which the symptoms progress is different for each individual. In some cases, other conditions can be responsible for symptoms like getting worse. These conditions include:

- infections
- stroke
- delirium

As well as these conditions, other things, such as certain medicines, can also worsen the symptoms of dementia. Anyone with Alzheimer's disease whose symptoms are rapidly getting worse should be seen by a doctor so these can be managed. There may be reasons behind the worsening of symptoms that can be treated.[42]

Stages of Alzheimer's disease

Generally, the symptoms of Alzheimer's disease are divided into 3 main stages.

Early symptoms

In the early stages, the main symptom of Alzheimer's disease is memory lapses. For example, someone with early Alzheimer's disease may:

- Forget about recent conversations or events
- Misplace items
- Forget the names of places and objects
- Have trouble thinking of the right word
- Ask questions repetitively
- Show poor judgement or find it harder to make decisions
- Become less flexible and more hesitant to try new things

There are often signs of mood changes, such as increasing anxiety or agitation, or periods of confusion.

Middle-stage symptoms

As Alzheimer's disease develops, memory problems will get worse. Someone with the condition may find it increasingly difficult to remember the names of people they know and may struggle to recognise their family and friends. Other symptoms may also develop, such as:

- increasing confusion and disorientation – for example, getting lost, or wandering and not knowing what time of day it is
- obsessive, repetitive or impulsive behaviour
- delusions (believing things that are untrue) or feeling paranoid and suspicious about careers or family members
- problems with speech or language (aphasia)
- disturbed sleep
- changes in mood, such as frequent mood swings, depression and feeling increasingly anxious, frustrated or agitated
- difficulty performing spatial tasks, such as judging distances
- seeing or hearing things that other people do not (hallucinations)Some people also have some symptoms of vascular dementiaBy this stage, someone with Alzheimer's disease usually needs support to help them with everyday living. For example, they may need help eating, washing, getting dressed and using the toilet.

Later symptoms

In the later stages of Alzheimer's disease, the symptoms become increasingly severe and can be distressing for the person with the condition, as well as their carers, friends and family. Hallucinations and delusions may come and go over the course of the illness, but can get worse as the condition progresses. Sometimes people with Alzheimer's disease can be violent, demanding and suspicious of those around them. A number of other symptoms may also develop as Alzheimer's disease progresses, such as:

- difficulty eating and swallowing (dysphagia)
- difficulty changing position or moving around without assistance
- weight loss – sometimes severe
- unintentional passing of urine (urinary incontinence) or stools (bowel incontinence)
- gradual loss of speech
- significant problems with short- and long-term memory
- In the severe stages of Alzheimer's disease, people may need full-time care and assistance with eating, moving and personal care.

Side effects and treatment of Alzheimer

Common side effects include the following:

- Dizziness
- Nausea
- Vomiting
- Diarrhea
- Loss of appetite
- Abdominal pain
- Salivation

Treatment

Individuals with Alzheimer's disease should remain physically, mentally, and socially active as long as they are able. It is believed that mental activity can slow the progression of the disease. Puzzles, games, reading, and safe hobbies and crafts are good choices. These activities should ideally be interactive. They should be of an appropriate level of difficulty so that the person does not become overly frustrated. Behavior disorders such as agitation and aggression may improve with various interventions. Some interventions focus on helping the individual adjust or control his or her behavior. Others focus on helping caregivers and other family members change the person's behavior. These approaches sometimes work better when combined with drug treatment for depression, mood stabilization, or psychosis. Alzheimer's disease symptoms can sometimes

be relieved, at least temporarily, by medication. Many different types of medications have been or are being studied in the treatment of dementia. Currently, the drugs used for Alzheimer's disease are not a cure, but they help slow down the rate of decline in some people. In many people, the effect is modest, and in others,[43] the effect is not noticeable. Certain drugs, such as anti-inflammatory drugs (ibuprofen), vitamin E, and hormone therapy (estrogen) have been used on a trial basis in people with Alzheimer's disease. Experts think these drugs might help based on what we know from research about Alzheimer's disease. None of these drugs have yet achieved widespread acceptance as treatment for the disease. The following sections discuss cholinesterase inhibitors and NMDA inhibitors, which have been approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe Alzheimer's disease. There is no cure for Alzheimer's, but number of different drugs are in use to treat the disease's symptoms. They target a couple different mechanisms in the brain and nervous system that lead to Alzheimer's-related dementia. Some drugs reduce the amount of enzyme that breaks down a crucial neurotransmitter chemical, while other drugs target the nerve cell receptors themselves. A number of existing medications and supplements are also under study. Scientists hope these substances can someday prove useful in combating Alzheimers.

CONCLUSION

This review summarized the current concepts on neurodegenerative pathways that may lead to a “domino” cascade of events leading to manifestation of AD. Aging and oxidative stress are currently recognized as key factors that cause the pathophysiological features of these diseases. The inevitable aging process may augment ROS formation and accumulation, which activate several neurodegenerative pathways and lead to neuronal loss. Multiple pathways have been recognized to cause AD, but these changes are not seen in all cases of AD. Treatment strategies can be achieved by targeting the specific pathways that were activated, such as halting the deleterious neuroinflammatory pathway, improving the clearance of aggregated protein by UPP, and augmenting the endogenous antioxidant enzyme level.

It is extremely important to understand the intricate details of disease mechanism, as this understanding allows researchers and clinicians to identify the right therapeutic approach and disease management at an early stage; late stage of AD usually has a lower success rate of treatment. To be diagnosed at an early stage of the disease, it is essential to define the biomarkers that correctly indicate the onset of the disease in patients. Disease biomarkers can also be used to monitor the severity of the disease and the response to prescribed drugs. Efforts to discover more diagnostic biomarkers should be encouraged and integrated with state-of-the-art approaches to experimental and clinical trial designs to discover suitable treatments for these diseases. Given the explosive amount of information on AD, we are sure that the discovery of an ideal therapeutic drug for AD will be achieved in the near future.

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