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Review Article

ALZHEIMER'S - A NEURODEGENERATIVE DISEASE; START TO END

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Abstract
Alzheimer's disease (AD) which is a progressive, irreversible, age-related, neurological and psychiatric disorder characterized by a progressive decline in memory, cognitive performance and loss of acquired skills leading to apraxia, agnosia, anomia and aphasia. The extra cellular accumulation of amyloid beta peptide, Intracellular hyperphosphorylation of Tau-proteins, Inflammatory reactions such as involvement of interleukins (IL-1 beta and TNF-alpha), excitotoxicity, oxidative stress and expression of COX and LOX are involve in the basic patho-physiology of AD. There are some neurotoxic chemicals such as streptozotocin and colchicines which are given intracerebroventricularly in rat's brain as animal model to induce Alzheimer's disease.

Keywords: - : Alzheimer's disease; amyloid beta; Tau protein and neuroinflammation

Introduction
Alzheimer's diseases (AD) is an irreversible, progressive neurodegenerative disorder that occurs gradually and results in memory loss, unusual behavior, personality changes, and a decline in thinking abilities (1). AD is accompanied by neuritic plaques (2), neurofibrillary tangles (NFTs) (3), and inflammatory changes (4). Neuritic plaques, also referred to as senile plaques, are extracellular deposits of amyloid-beta (Aβ) peptide (5). Neurofibrillary tangles are intracellular aggregates of paired helical filaments (PHFs) composed primarily of hyperphosphorylated tau protein (PHF-tau) (6). Aβ deposition and presence of paired helical filaments have been correlated with neurodegenerative changes and cognitive abnormalities (7). Inflammatory mediators and other immune system constituents are present near areas of plaque formation, suggesting that the immune system also plays an active role in the pathogenesis of AD (8). Glial cells (microglial cells and astrocytes) (9), cytokines (e.g., interleukin-1, Interleukin-6 and TNF-α) (10), oxidative stress (11) mitochondrial dysfunction (12), excitotoxicity, increased expression of COX/LOX and components of the classic complement cascade are also markedly increased in plaque-infested areas (13). Inflammatory mediators have been shown to increase Aβ aggregation and toxicity, chronic production of cytotoxic agents and free radicals through activated microglia, accelerating the neurodegeneration process (14).

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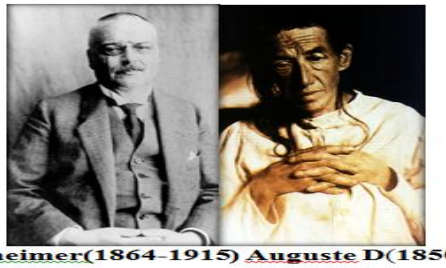
Alzheimer's disease - a historical perspective
The references to senile dementia were first recorded around 600 B.C. But it was only after about 200 years that Gallen, who had achieved a pinnacle of Greek medicine, actually added the term **"morosis"** (dementia) to the list of mental diseases and included old age as one of the stages in which it occurred (15). Alois Alzheimer (1864-1915), a German neuroscientist, studied a clinical case of 55 years old woman by the name Auguste Deter who was suffering from dementia and admitted to the mental asylum in Frankfurt. Later, when she died on April 8, 1906, her brain was sent for examination. In November of the same year, Alzheimer described a peculiar disease of the cerebral cortex and published his presentation in 1907. This was the first case of AD described by Alois Alzheimer (5).



Alois Alzheimer(1864-1915) Auguste D(1850-1906)

Alzheimer is credited for his extraordinary clinical observations in this specific case of Auguste D. The patient′s illness was unique because of her age, speed of the disease's progression and neuropathological findings. Alzheimer′s discovery of senile plaques in presenile dementia was significant (16).

Epidemiology Of Alzheimer′s Disease

Alzheimer′s disease is the leading cause of senile dementia. It poses serious health problem of pandemic proportion. It is the fourth leading cause of death in the developed world. Currently, it is estimated that worldwide there are 40 million people affected by AD and it is predicted that by the year 2030 this number will reach in excess of 60 million. The prevalence of AD seems to be rising exponentially at least between 65 and 85 years of age, doubling with every 5 years of age interval.

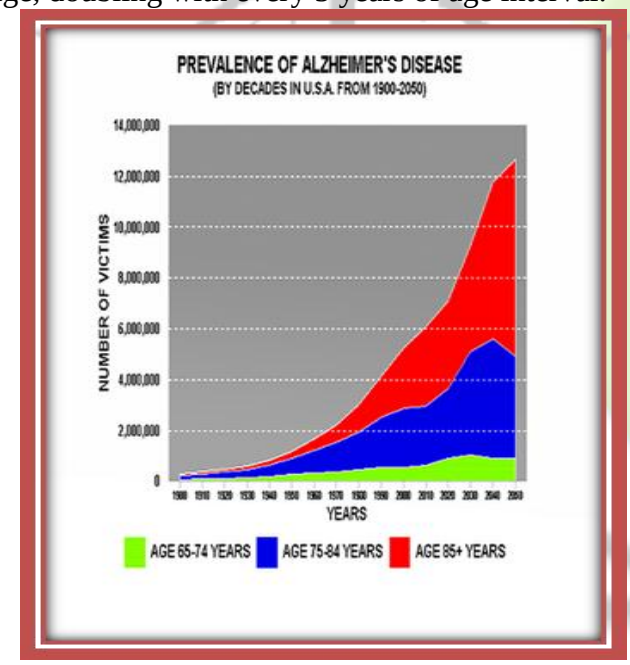


Fig.1: Prevalence of Alzheimer's Disease

Symptoms Of Alzheimer's Disease

Etiology of AD is rather complex and mostly includes symptoms of the neuropsychiatric diseases. Most prominently, dementia is the foremost clinical symptom observed with aging followed by noncognitive symptoms and physical deterioration at the end. It is a condition that spreads throughout the brain producing a pattern of cognitive and noncognitive symptoms discussed below.

Clinical Symptoms

The clinical Symptoms of AD are differentiated into three broad categories, namely cognitive, noncognitive, and physical deterioration (18).

Cognitive symptoms

Severe memory deficits contribute to deficiencies in non-memory cognitive domains such as language, conceptualization and are associated with deficits in abstract reasoning, visuospatial functioning and other executive functions (19). Moreover, language difficulties characterized by anomia, agnosia, aphasia, complete mutism occur in advanced stages of AD.

The other cognitive symptoms are impaired visuospatial skills and apraxia, poor judgement, and evidence of carelessness, particularly self-neglect, and personality changes which include self centeredness, withdrawal, increased passivity and agitation, mood changes, disorientation, excessive confusion.

Noncognitive symptoms

Cognitively impaired patients experience many psychopathological symptoms and these may cluster together as "symptom complexes" or syndromes (19) as follows.

a. Disturbances of Mood

Major depression, reactive dysphoria, anxiety, irritability, restless overactivity, agitation, catastrophic reaction are the common relayed symptoms. Other mood related symptoms appear less often such as phobias, apathy, mania (20).

b. Delusions

Delusion is the second common psychopathologic symptom. It occurs in the early to middle course of illness (2-4 years after onset on average), when dementia is mild or moderate and dissipates when dementia is severe (21).

c. Hallucinations

About 25% of AD patients experience hallucinations during the course of their illness. Visual and auditory hallucinations are most common and somatic, olfactory and tactile hallucinations are less frequent (22).

d. Behaviors

Learned behaviors

Deterioration of learned behaviors arises 2 to 3 yrs after the onset of cognitive symptoms. Many of the impairments of learned behaviors can be described as aphasia and apraxia (4).

Stereotyped behaviors

The behaviors driven by internal cues include sleep disturbances, ingestive behaviors which include decreased appetite, anorexia, weight loss, sexual apraxia and repetitive motor activity (23).

. Undefined behaviors

Agitation, wandering (24).

Physical deterioration

As the disease progresses, it leads to physical deterioration and patients become bedridden with impaired physical activity. Seizures and myoclonus may affect up to 10% of patients in late stage of the disease (25).

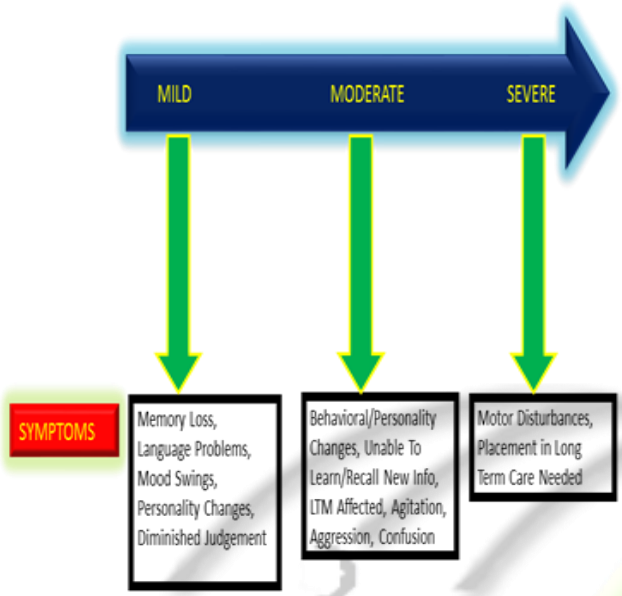


Fig.2: Stages of Alzheimer's diseases

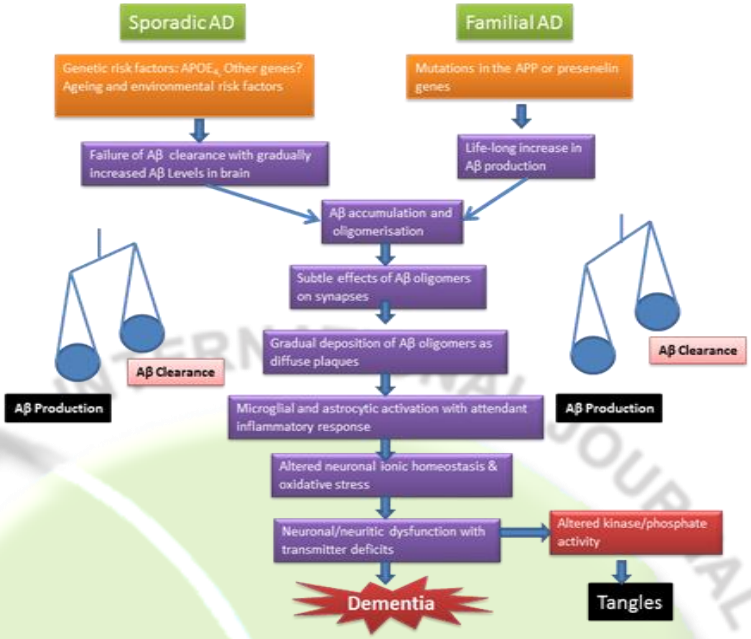


Fig.3: Pathway of Sporadic and Familial Alzheimer's disease

Pathophysiology of Familial and Sporadic forms of Alzheimer Disease

Although neurological features of FAD and Sporadic AD (SAD) are very similar, the trigger to pathogenesis is the result of different degrees of reaction to common cerebro-metabolic insults. In the case of FAD, development of disease is directly linked to genetic mutations. Mutations in three different genes i.e. PS-1, PS-2 and APP, results in increased production of Aβ, particularly the longer Aβ1-42 species, either by modifying the substrate (APP) or by modulating the activity of the γ-secretase enzyme that releases the insoluble form of Aβ from full-length AP(26). Alternatively, in the more common sporadic AD, a genetic locus of chromosome 19 [coding for the apolipoprotein E (ApoE)] is associated with increased susceptibility (27). In the brain tissue of individuals with sporadic AD, there is a remarkable reduction in the ApoE receptor LR11/SorLA, mainly in vulnerable areas of the cortex and hippocampus**.** LR11 is a member of the low-density lipoprotein receptor (LDL-R) family (28). A study indicates the involvement of lipoprotein receptors and cholesterol metabolism in the regulation of amyloid-β generation and links between cholesterol and neurodegeneration. The LR11 is markedly downregulated in patients with sporadic AD but it is not clear whether LR11 loss occurs downstream of the AD pathologic cascade or if reduction in LR11 expression could be a contributing factor to the AD process (29).

However, more than 70% of the AD cases in the general population are unrelated to any of these four genes, suggesting that disruption of metabolic processes may be responsible for early occurence of AD. The disruption may be occurring due to the interaction among insulin receptor desensitization, mitochondrial dysfunction, oxidative stress, dysregulation of calcium homeostasis and reduced energy metabolism - the so called mitochondrial spiral (30) reported for the first time qualitative determination of metabolic differences between the two phenotypic subtypes of AD. Their study presented that the patients with FAD show reduced metabolic rate of glucose (MET glu) in comparison with the SAD patients. But, the absolute MET glu measurements could provide useful information about the distinction between FAD and Sporadic AD. Indeed, the MET glu declines in such AD pateints even before any signs of memory impairment or brain atrophy are detectable (31). In fact, some other studies have reported that some of the cellular metabolic alterations are observed in early stages of sporadic type of AD including brain insulin receptor desensitization, decreased glucose utilization and energy metabolism. At molecular level, the overactivation of protein kinase GSK-3 is reported in subjects with sporadic AD (32). Recently, the glutamate excitotoxicity is also observed in SAD patients. Some of these pathological aspects of sporadic AD patients are very much similar to ICV-STZ induced Alzheimer's type of dementia in animal models (33). Thus, ICV-STZ animal model may be a relevant model for sporadic type of AD

Pathological features of Alzheimer's disease

The pathological hallmarks of AD are cholinergic neuronal loss, extracellular deposition of senile plaques, widespread formation of neurofibrillary tangles (NFTs) and chronic neuroinflammation (34). At the cellular and molecular levels, a variety of inflammatory processes have been reported in AD and they are the ones that are mainly associated with neuropathological lesions (i.e. plaques and

neurofibrillary tangles) (35).In particular, inflammatory cells such as astrocytes and microglia are activated in areas of the brain affected by amyloid plaques and tau pathology which release several proinflammatory mediators including cytokines, chemokines, prostaglandins, leukotrienes (LTs), reactive oxygen species (ROS) and reactive nitrogen species (RNS) (36-40). Besides, neurotransmitter abnormalities, increased MAOB activity and abnormalities in glutamate pathway of cortex and limbic structures lead to excitation and loss of neurons and cause dysfunction of brain areas such as cerebral cortex, limbic, hippocampus, median raphe neuclei and locus ceruleus, all of which are involved in memory and cognitive functions. All of these pathological features actively contribute to the pathogenesis of AD, and are discussed as follows.

Amyloid beta and its toxicity

Alzheimer's disease is caused by the cerebral accumulation and cytotoxicity of amyloid β-protein. The amyloid cascade hypothesis was first formulated in 1991 (41) and centers around the Aβ peptide which is the main component of plaques and play an early, critical role in the diseases process (42)

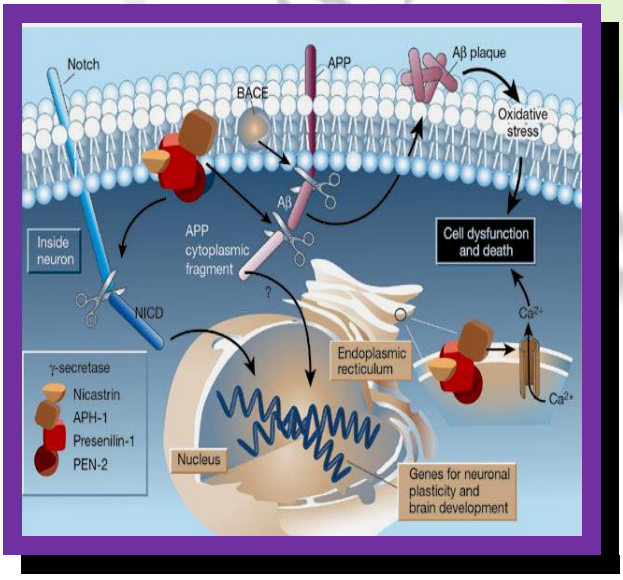


Fig.4: Amyloid precursor protein, Amyloid-beta production, Aβ plaque formation and neuronal cell death

Aβ accumulation, meaning a rise in its steady state cerebral levels, is the central event in the pathogenesis of AD (43). The mainstay of the amyloid β-protein hypothesis of AD is that gradual and chronic imbalance in the production versus the clearance of Aβ leads to a slow rise in its steady state levels in brain tissue which, in turn, leads over years and decades to the complex molecular and cellular changes of AD (44). Progressive cerebral accumulation of amyloid β protein initiates a complex multicellular cascade that includes microgliosis, astrocytosis, neuritic dystrophy, neuronal dysfunction and synaptic insufficiency that results in unfavourable neurotransmitter alterations and impaired cognitive functions. The mechanisms that trigger Aβ deposition and its subsequent transformation to neuritic plaques occur in selected brain regions i.e. in limbic areas and associated cortices. The APP mutation leads to an increase in levels of Aβ(1-42) or total Aβ. The majority of familial AD mutations in genes encoding APP increase Aβ production promoting Aβ deposition in brain (45).

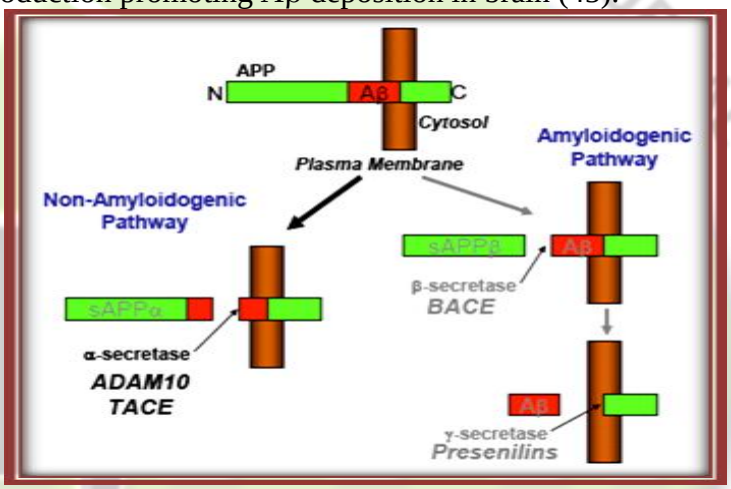


Fig.5: Amyloidogenic and Non-Amyloidogenic pathways

Tau protein and its tangling

The intraneuronal accumulation of paired helical filaments in the form of neurfibrillary tangles is another prominent hallmark of the neuropathology of AD. Structurally, neurofibrillary tangles consist of paired helical filaments (PHF) and occasional single straight filaments, mainly containing a hyper or abnormally phosphorylated form of microtubule associated protein called(46).

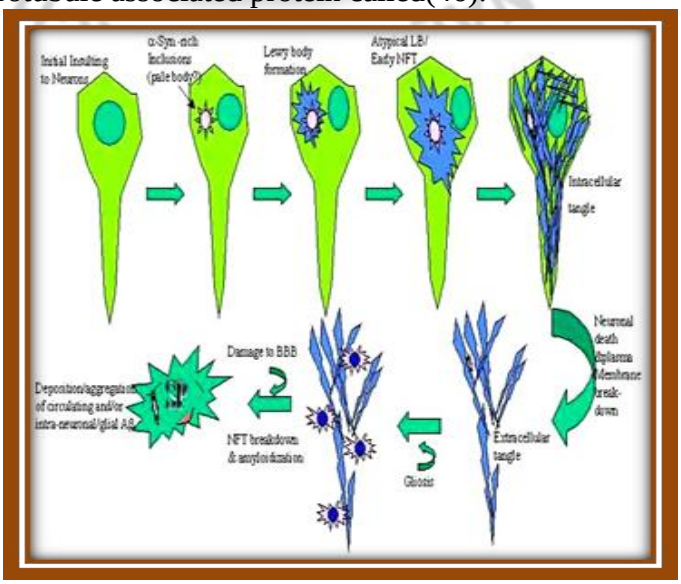


Fig.6: Progression of tau tangle formation

Phosphorylated tau protein, if not dephosphorylated, is unable to bind to microtubules, undergoes polymerization into straight filaments and then cross links by glycosylation to form PHF-tau. Tau aggregates are conjugated with ubiquitin and are located not only in neurons but also in many dystrophic neurites within and outside the neuritic plaques (47-50). Neurofibrillary tangles in the AD are generally found in large numbers, particularly in entorhinal cortex, hippocampus, amygdala and associated cortices of the frontal, parietal and temporal lobes, and certain subcortical nuclei that project to these regions (51-53). The extent of neurofibrillary pathology particularly, the number of cortical neurofibrillay tangles, correlates positively with the severity of dementia (54).

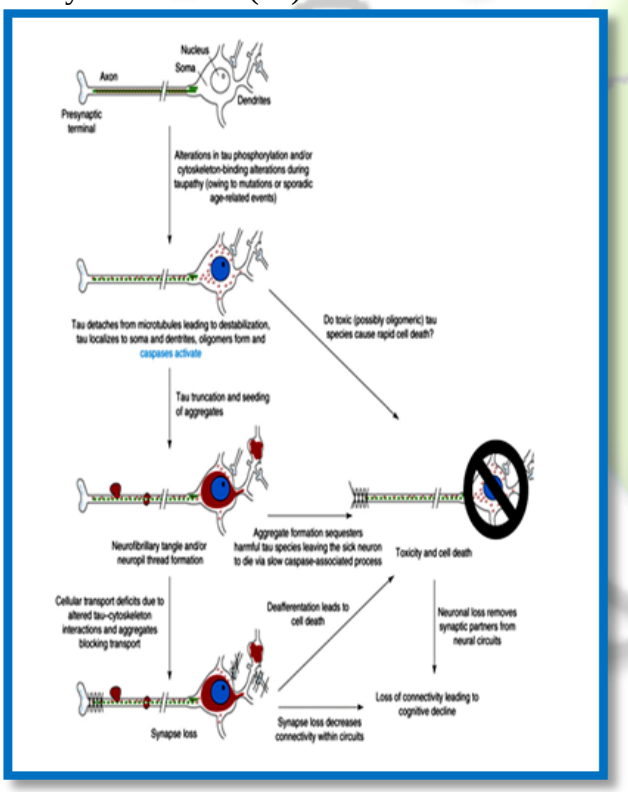


Fig.7: Tau Tangle formation leading to neuronal cell death and cognitive decline

Neuroinflammation

Neuroinflammation is a prominent feature of AD pathology. It plays a central role, influencing and linking β-amyloid deposition with neuronal damage and clinical disease (55). Alzheimer's disease is a multifactorial disorder, which appears to encompass both neurodegeneration and neuroinflammation as pathological hallmarks. At the molecular and cellular levels, a variety of inflammatory processes associated with neuropathological lesions (i.e plaques and NFT) are observed in AD brain.

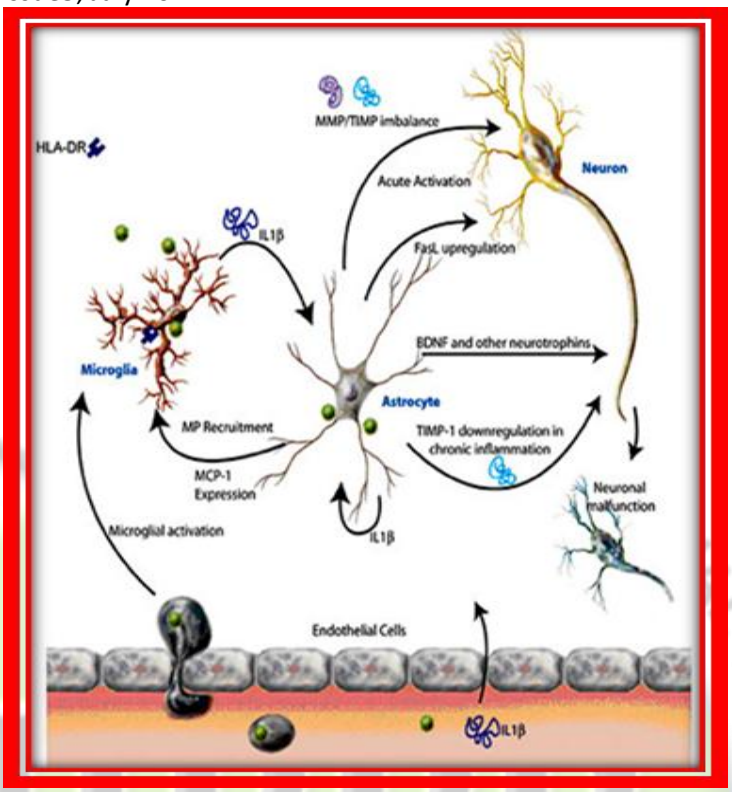


Fig.8: Role of various inflammatory cytokines in progression of neuronal death

Inflammatory cells, such as microglia and astrocytes are activated in areas of the brain affected by amyloid plaques and tau pathology (56-60). Reactive microglia and astrocytes play an integral role in the initiation and exacerbation of CNS inflammation. Both types of cells demonstrate a reactive phenotype characterized by the release of various pro- and anti-inflammatory mediators inducing cytokines, oxygen species and reactive nitrogen species (60,61).

2.5.4 Cerebral Energy failure

Advancing age is associated with decreased metabolism frontal areas, temporal and parietal cortices (62). Furthermo reduced brain glucose metabolism and increased oxyg consumption have been observed in patients with AD also (6 Although glucose is the primary energy substrate, brain ce metabolize ketones during reductions in blood glucose lev (64) through neurons are known to utilize ketone bodies even the presence of glucose also. However, a supplement ketogenic diet proves to be beneficial in experimental models Alzheimer's disease (65,66), further supporting the evidence overall energy failure in AD. Cerebroenergetic failure ma therefore, be the result of impaired glucose utilization, insu receptor signaling and lipid homeostasis(67).

AD patients have further been reported to have lower CSF insulin levels and reduced insulin-mediated glucose disposal when compared to healthy control subjects (70) which suggests that AD could be viewed as a ''type III diabetes'' due to loss of CNS insulin (72-77). In the brain, insulin serves as a neuromodulatory and neuroendocrine molecule in addition to its usual metabolic function, playing a significant

role in neuronal growth and survival. Insulin signaling plays an important role in synaptic plasticity and in spatial learning (78). Synaptic plasticity is likely to be dependent on the capacity of neurons to meet energy demands to maintain ionic homeostasis (79). Emerging evidence indicates that events associated with energy balance can impact synaptic and cognitive function (80). Impaired cerebral energy metabolism can lead to neuronal damage or facilitate the deleterious effects of some neurotoxic agents such as glutamate (81-83). The reduction in cerebral energy metabolism appears early in AD, possibly even preceding the onset of clinical symptoms in some patients and

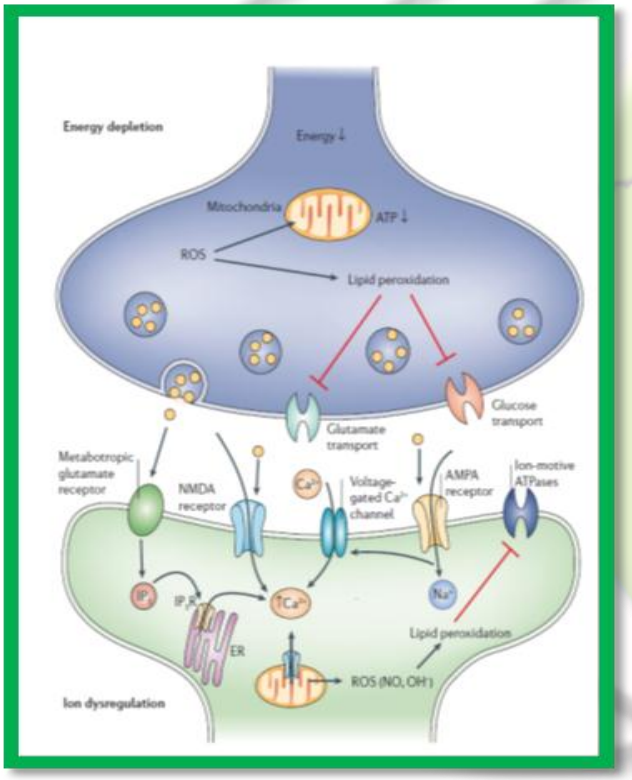


Fig.9: Cerebral energy failure pathway

increases in magnitude as the disease becomes mc severe (84). Moreover, decline in cerebral energy i reduction in cellular ATP has been implicated calcium overload, excitotoxicity, oxidative stress, a in synaptic dysfunction which leads to cogniti decline (85-87).

Oxidative stress

Alzheimer's disease is a heterogeneous disease with a complex pathophysiology and involves multiple overlapping and redundant pathways of neuronal damage. In addition to the pathological hallmarks of disease, which include senile plaques and neurofibrillary tangles, AD brains exhibit a number of abnormalities such as loss of synapses, gliosis, microglia activation, signs of inflammation and damage secondary to oxygen radicals (88-91).

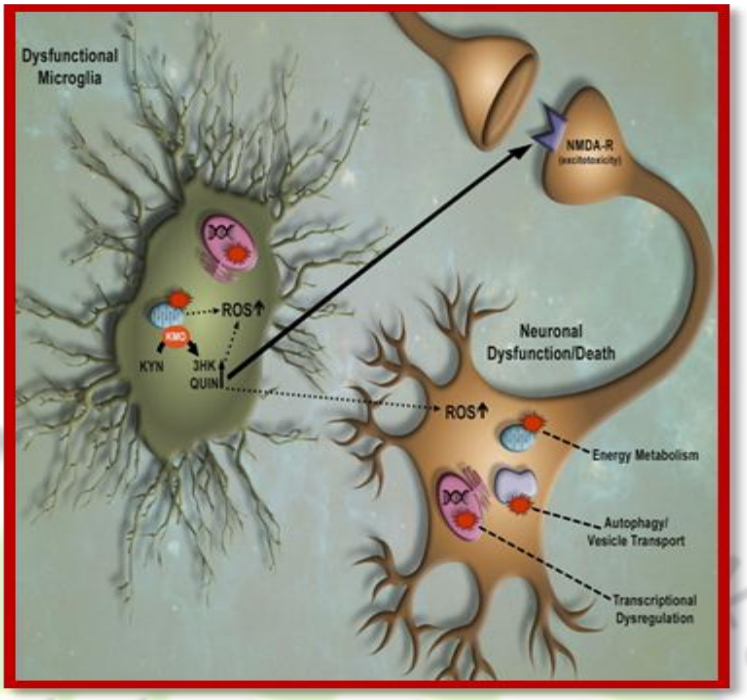


Fig.10: Activation of Glial cells and NMDA receptor via ROS

Progressive degeneration of a subset of neurons is another pathologic hallmark of adult onset of neurodegenerative disorders such as AD, Parkinson′s disease and Amyotrophic Lateral Sclerosis in adults (92). Free radicals are the main mediators of neuronal death in neurodegenerative disorders. Oxidative stress can be a final common pathway in various forms of neuronal cell death, both for inducing a wide variety of acute and chronic neurological diseases as well as for normal aging (93).

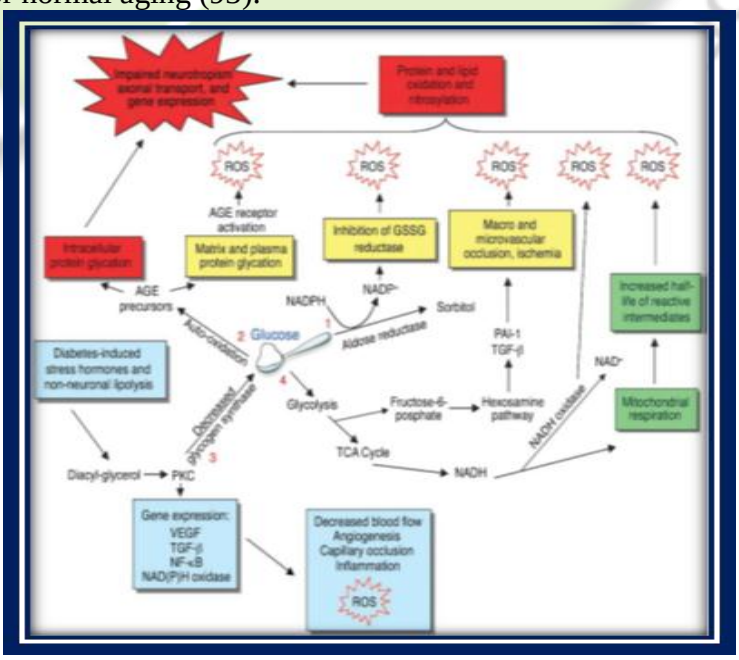


Fig.11: Biochemical alterations in AD brain mediated by ROS

Excitotoxicity

Excitotoxicity, the term coined by Olney in 1969, occurs due to excessive release of excitatory amino acid glutamate and

overactivation of their receptors (94). During acute and chronic neurodegenerative disorders, disruption of energy metabolism impairs the clearance of glutamate due to transporter dysfunction (95). Excitotoxicity propagates in a chainlike manner as dying neurons release more glutamate to neighboring neuronal cells, particularly during ischemia and AD (96).

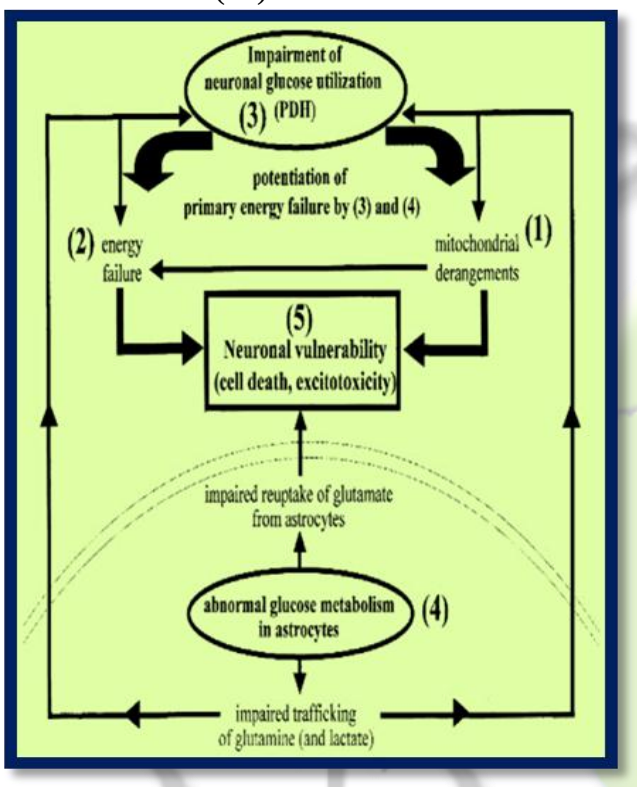


Fig.12: Excitotoxicity pathway leading to neuronal death

Glutamate concentration evokes damage by decreasing resting membrane potential and intracellular buffering of Ca^{++} ions (97). Glutamate release causes excessive influx of Ca^{++} through overactivation of NMDA and AMPA receptors and consequently free radical production that contributes to neuronal injury and cell death . Improving energy metabolism can thus prevent glutamate toxicity and be a useful approach in correcting neurodegenerative disorders(98).

Neurotransmitter deficits

The cholinergic system has received the lion's share of attention in AD pharmaceutical research. The cholinergic deficit also exists in other neuronal cell damage pathways. For example, serotonergic neurons of the raphe nuclei and noradrenergic cells of the locus ceruleus are lost, while monoamine oxidase type B activity is increased. Monoamine oxidase type B is found predominantly in the brain and in platelets, and is responsible for metabolizing dopamine. In addition, abnormalities appear in glutamate pathways of the cortex and limbic structures, where loss of neurons leads to a focus on excitotoxicity models as possible factors contributing to AD pathology (99).

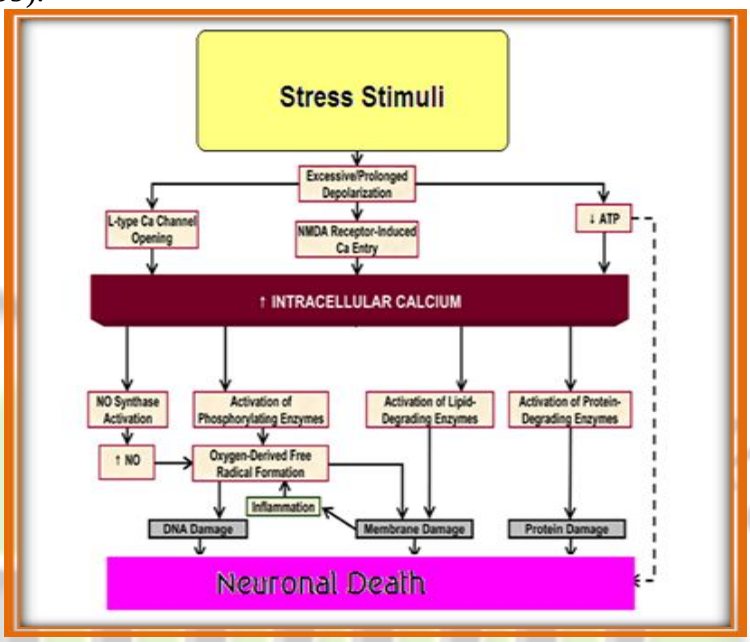


Fig.13: Mechanisms of neuronal cell death caused by increased intracellular calcium levels

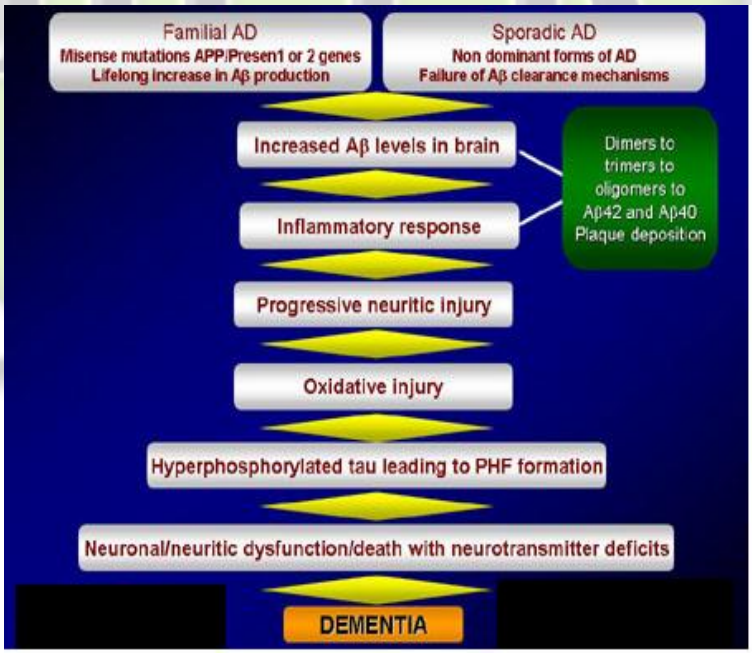


Fig.14: Neurotransmitter deficit in dementia of Alzheimer type

Glutamate is the major excitatory neurotransmitter in the cortex and hippocampus. Many neuronal pathways essential to learning and memory use glutamate as a neurotransmitter, including the pyramidal neurons (a layer of neurons with long axons carrying information out of the cortex), hippocampus, and entorhinal cortex. Glutamate and other excitatory amino acid neurotransmitters have been implicated as potential neurotoxins in AD (100). If glutamate is allowed to remain in the synapse for extended periods of

time, it can destroy nerve cells.Toxic effects are thought to be mediated through increased intracellular calcium and accumulation of intracellular free radicals (101-103). The presence of βAP renders cells more susceptible to glutamate-mediated excitotoxicity *in vitro*. Dysregulated glutamate activity is thought to be one of the primary mediators of neuronal injury after stroke or acute brain injury. Although intimately involved in cell injury, the role of excitatory amino acids in AD is as yet unclear. However, blockade of N-methyl-D-aspartate (NMDA) receptors decreases activity of glutamate in the synapse and may lessen the degree of cellular injury in AD (104).

Cognitive abnormalities

Hippocampus is an area known to play role in spatial memory formation (105). Impairment of long term potentiation (LTP) in CA1 region of hippocampus has been noted to affect memory (106-110). Activation of NMDA receptor/channel complex and post synaptic calcium dependent second messenger system are necessary for LTP in the area of CA1 (111,112). Synaptic plasticity is a term that describes long-lasting changes in the efficacy of synaptic transmission (113). LTP is widely accepted physiological mechanism of learning and memory (114-117) and it can be induced by brief high frequency stimulation (HFS) of afferent fibers of hippocampus neuron which release glutamate from presynaptic neurons to activate post synaptic glutamate receptors (118,119) such as AMPA (120), NMDA and metabotropic receptors (121-124).

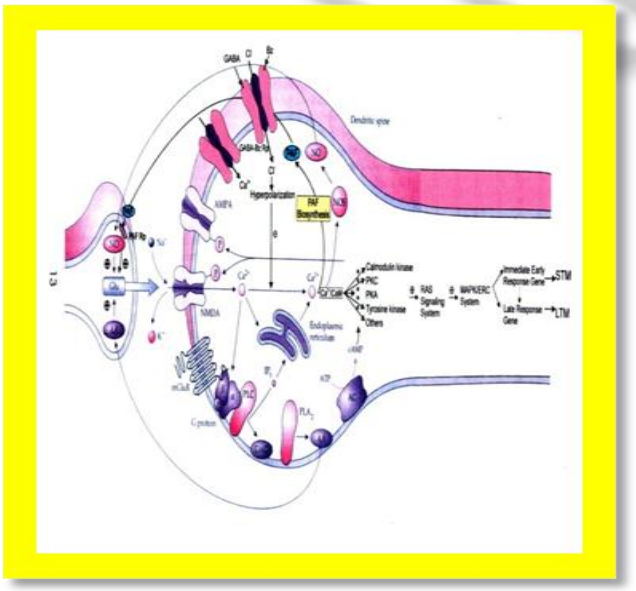


Fig.15: Molecular Mechanism of cognitive abnormalities

Summarising the pathophysiology of AD, it may be stated that it is an age related (125-129), chronic neurodegenerative disorder characterized neuropathologically by the presence of extracellular senile plaques and intracellular neurofibrillary tangles (130). Senile plaques are composed of deposits of Amyloid-beta (Aβ) (131-134) associated with dystrophic axons and dendrites as well as activated microglia and reactive astrocytes (135-137). The neurofibrillary tangles are composed of hyperphosphorylated microtubule-associated protein, *tau*, resulting in impairment of interneuronal communications (138). Aβ is a 42 amino acid peptide derived from processing of the transmembrane amyloid precursor protein in normal conditions. The earliest morphological change - the deposition of Aβ - appears due to abnormal Amyloid metabolism that forms fibrillar type of Aβ whose aggregation and deposition leads to (139,140) formation of neuritic plaques which has been shown to be neurotoxic to the neurons. This initiates the generation of free radicals and activation of microglia resulting in oxidative stress, neuroinflammation (141). Free radical generation causes mitochondrial damage leading to ATP depletion, energy failure (142), excitotoxicity (143) and finally exacerbating the disease process. The neuritic plaques are located within various brain regions but the hippocampus, cerebral cortex and amygdala are particularly vulnerable resulting in progressive cognitive disturbances (144) including memory, judgment, decision-making and other behavioral changes like physical orientation and language (145). The other neuropathological features include neuropil threads, Hirano's bodies, granulovacuolar bodies and cerebral amyloid angiopathy (146).

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