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ALZHEIMER'S DISEASE: PATHOLOGICAL HALLMARKS OF ALZHEIMER'S DISEASE

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ABSTRACT: Dementia is a collection of symptoms, including memory loss and cognitive impairment, that cause neuronal disruption and lead to certain mental illnesses. The most common cause of dementia is Alzheimer's disease (AD). Potential causes of illness extension include tau aggregation, amyloid beta build-up outside of neurons, and the formation of neurofibrillary tangles (NFTs) inside neurons. At one point in time, Alzheimer's disease was the most common illness worldwide. The majority of research indicates that ROS (Reactive Oxygen Species) play a significant role in neurodegeneration and, eventually, Alzheimer's disease. Amyloid-peptide increases in Alzheimer's disease led to an increase in ROS production, which kills neurons. A transcription factor called Farnesoid X Receptor (FXR) regulates inflammation, oxidative stress (OS), and the brain's metabolism of fats and carbohydrates. Nuclear erythroid 2 related factor 2 (Nrf2) is a transcription factor that regulates the production of many antioxidant genes and is an essential regulator of neural defence against OS. According to certain studies, Nrf2 activation can regulate the expression and activity of FXR in the liver, suggesting that these two transcription factors work in concert. Even while the exact relationship between FXR and Nrf2 in the brain is not entirely understood, it is likely that comparable interactions occur in this case. Activating the FXR and Nrf2 pathways may, in general, decrease oxidative stress and inflammation in the brain, making them appealing therapeutic targets for neurological disorders associated with inflammation and OS.

INTRODUCTION: The major prevalent aspect of dementia is called Alzheimer's disease (AD), which can be usually characterized as a slowly progressing neurodegenerative condition and was named after the German psychiatrist Alois Alzheimer [1].

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It is characterized by the development of intracellular neurofibrillary tangles made primarily of hyperphosphorylated tau and extracellular plaques made primarily of amyloid (A), as well as an increasing neuronal loss, especially in the cerebral cortex and hippocampus, which impairs cognitive function, and their etiology is currently unclear. In fact, after much research, it is still unclear how Aβ accumulation and NFT production and deposition work, and there is no cure for this condition. Due to this, a number of signaling pathways associated with specific pathophysiological processes have been researched and assessed as potential targets for cutting-edge

use of therapeutic approaches in treatment of AD in recent years. Dementia prevalent in South Asia was 1.9% in 2005; it is anticipated to rise to 3.6 million by 2020 and 7.5 million by 2040 [2].

A rising proportion of people in India are getting older as a result of longer lifespan and lower fertility rates. Those older than 60 years old are anticipated to make up 19.1% of the population by 2050[3]. On basis of mild, moderate, and severe signs and symptoms are given in this [4] **Table 1.**

TABLE 1: SIGN AND SYMPTOMS OF AD

Sign And Symptoms	
Memory Loss	Aphasia (impairment of language)
Language Impairment	Amnesia (forgetfulness),
Mood Swings	Loss of visuospatial function
Behavioral Changes	Praxis (perform purposeful movements)
Inability To learn New Information	Confusion
Agitation	Motor disturbances
Aggressive Behavior	Ataxia

The severity of cognitive impairment and the histopathological changes are the key criteria used to classify AD clinically. Typically, four steps are mentioned [5, 6].

Preclinical: As there aren't any obvious symptoms during this stage, it's frequently disregarded. Mild cognitive impairment is the typical classification. The hippocampus and entorhinal cortex are the first brain compartment to experience pathological alterations during this phase (later).

This stage's subjects exhibit modest impaired memory with comparatively sparse long-term memories from a symptomatologic perspective. There is no obvious impediment to their usual tasks.

Mild Alzheimer's disease: Behavioral abnormalities begin to appear in mild Alzheimer's disease at this stage. At this stage, the cerebral cortex begins to experience pathological changes. From a symptomatologic perspective, there is memory loss along with loss of the ability to retain newfound knowledge, forget about things and meetings, followed by a decline in problem-solving, decision-making, and executive functioning. Together with these symptoms, patients exhibit personality alterations and changes in mood, and a lack of spontaneity.

Moderate Alzheimer's disease: The symptoms worsen throughout this stage. Other areas responsible for language, thinking, and sensory analysis are affected by the pathological injury (cerebral cortex). Aside from a worsening of the symptoms from the earlier stages, behavioural issues and a propensity for social withdrawal start to show up. Language dysfunction and a decline in visual-spatial abilities follow. It should be noted that subjects struggle to identify their own loved ones at this time.

Severe Alzheimer's disease: that is severe: During this stage, patients entirely lose their independence in daily tasks. It is thought that all parts of the cortex are affected at this point by the pathological deterioration. When the affected person's cognitive abilities are at their lowest point, other systemic symptoms such as olfactory and autonomic dysfunction, sleeping problem, and extra pyramidal motor symptoms such as parkinson's disease symptoms and akathisia begin to appear.

NOTE- Several staging systems, like the one Braak & Braak introduced in 1996, were created for AD. This concept divides the course of AD into six stages based on topographical staging of neurofibrillary tangles. The Reagan Institute and National Institute on Aging's neuropathological criteria for the diagnosis of AD include this Braak's stage [6].

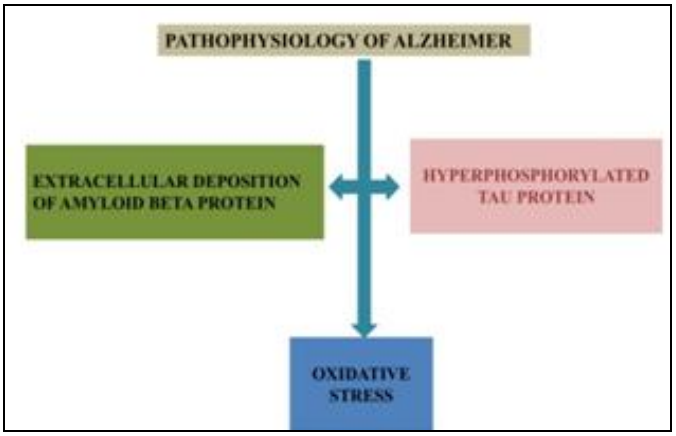

FIG. 1: PATHOPHYSIOLOGY OF AD

Pathophysiology of Alzheimer Disease: The accumulation of improperly folded Amyloid β and phosphorylated tau-proteins patients' brainsis causally linked to degeneration of neurons, according to a considerable body of evidence from the previous 30 years of study on Alzheimer

disease [9]. The extracellular plaque deposits of the Aβ and neurofibrillary tangles of the microtubule binding phosphorylated protein tau are two characteristic pathologies essential for an Alzheimer disease (AD) diagnosis **Fig. 1** [8].

Amyloid Beta Formation: Amyloid plaques, Senile amyloid plaques, or "miliary foci" are extracellular accumulations of the Aβ-40 &42peptides brought on by irregular sequencing of the amyloid precursor protein (APP) by the β & ϒ-secretases and a disequilibrium in the pathways for production and clearance, as stated by Alzheimer disease **Fig. 2** [10]. In healthy neurons, α & β-secretases break down APP, which has three domains: inside of the neuronal cell, in the neuronal cell membrane, and on the outside of the neuronal cell. During digestion, certain soluble polypeptides are created that can subsequently be disassembled and recycled inside the cell.

But, when β & ϒ-secretases work together, things go wrong. During this digestion process, the amyloid-beta peptide, an insoluble peptide, is formed (Aβ) [11]. During this digestion process, the amyloid-beta peptide, an insoluble peptide, is formed (A-beta). The amyloid beta plaques, may result from the aggregation of amyloid-beta peptides, are detrimental to the health of the cell [12].

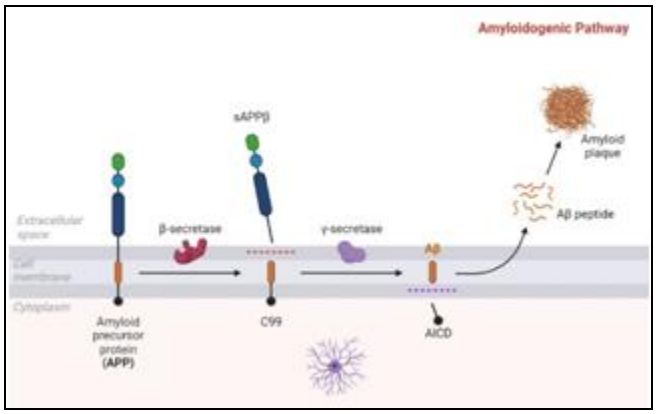

FIG. 2: AMYLOID BETA FORMATION

Neocortical early deposits can be detected (phase 1). A plaque then develops in limbic areas such the amygdala, cingulated gyrus, subiculum, and entorhinal cortex (phase 2). Aβ deposits in subcortical regions, such as the hypothalamus and basal neurons, indicate further development (phase 3). Moreover, plaques are visible in the cerebellar cortex in cases that are at the latter stages of the disease, affects the midbrain, pons, and medulla oblongata in the brainstem (phase 4), and in advanced cases, the cerebellar cortex as well (phase 5). Phase 1 and 2 were primarily seen in asymptomatic people, but phases 4 and 5 were connected to the existence of dementia [13]. Research findings of familial Alzheimer disease cases with APP, PSEN1, or PSEN2 alterations provide the most conclusive evidence for Aβ accumulation. Being the precursor to Aβ peptides, APP influences the breakdown and accumulation of Aβ peptides. PSEN1 and PSEN2 are catalytic subunits of secretases that cleave APP. PSEN mutations produce low effective APP processing and production of Aβ peptides that are longer and more hydrophobic, contrary to what was previously understood [9].

TAU Pathology: The brain neurons axons have highest levels of tau protein expression, although it is also present in oligodendrocytes, non-neural tissues, and the soma to dendritic portion of neurons [14].

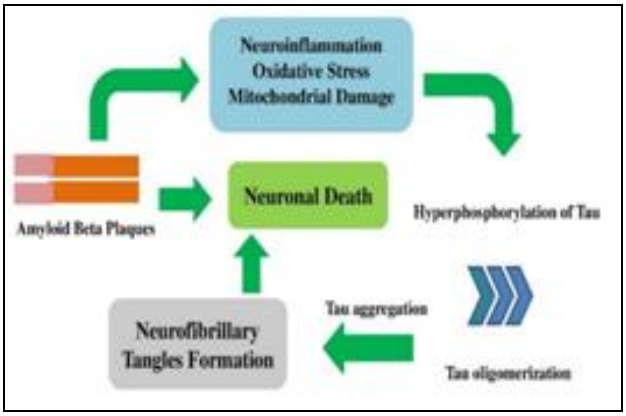

FIG. 3: TAU PHOSPHORYLATION (NORMAL AND DISEASE CONDITION)

The microtubule-attaching protein by assisting in the maintenance of stable axonal microtubules (MTs) in the brain, tau regulates axon transportation and development. Post-translational modifications (PTMs), primarily phosphorylation, govern Tau's binding to MTs as well as a number of other, less well-known roles [15]. Phosphorylation is one posttranslational change that can result in neurotoxicity and aggregate formation [16]. There are 85 potential sites of the phosphorylation of serine (S), threonine (T), and tyrosine (Y) in the phosphorylated protein tau. tau's proline-rich domain, which is on each side of the microtubule-binding domain, contains a large number of the

phosphorylated tau residues [17]. Neurons become malnourished as a result of hyperphosphorylation of particular amino acids in tau proteins, which leads to cell death in AD due to abnormalities in the cytoskeleton and transport system. The development of AD and other tauopathies, as well as intracellular neurofibrillary changes, are thus greatly influenced by hyperphosphorylated tau [18].

Tau goes through a number of post-translational alterations prior to the formation of tangles, which differ from the typical tau found in healthy brains. These modifications include hyperphosphorylation, acetylation, N-glycosylation, and truncation. Tau post-translational alterations promote tau misfolding and inhibit MT- tau from binding [19].

Microtubules function similarly to railroad rails in that they transmit nutrients and other chemicals. Tau-proteins serve as "ties" that hold the microtubule structure together. Tau proteins become knotted in Alzheimer disease, causing the microtubule structure to become unstable. Cell death occurs when axonal transport is disrupted **Fig. 3**.

Oxidative Stress: The mitochondrial process of oxidative Phosphorylation is a main source of generation of adenosine triphosphate (ATP). Free radicals are often referred to as reactive nitrogen species (RNS), ROS, and radicals with centres on carbon and Sulphur are produced [20]. Thus, the significance of OS in the both condition, acute and chronic brain stroke, traumatic brain damage, and neurodegenerative illnesses pathologies [21].

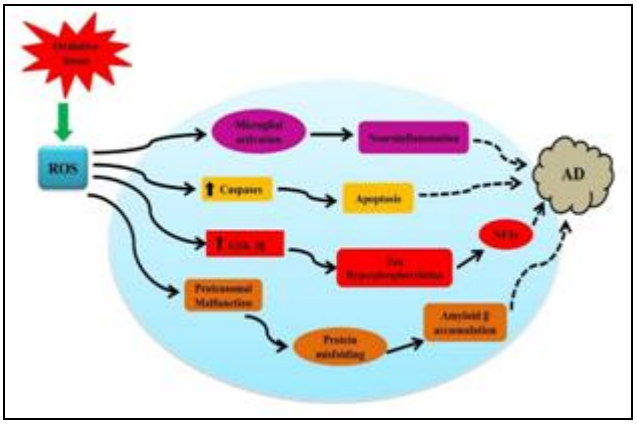

FIG. 4: ELECTRON TRANSPORT CHAIN AND ROS FORMATION

The free radical production is inextricably linked to metabolism and other enzymatic processes. Mitochondria (intracellular) and inflammation (extracellular) are the main producers of free radicals. These reactive compounds can damage DNA, proteins, and lipids when anti-oxidative processes are out of balance, leading to cell cytotoxicity and tissue injury. These mechanisms are tightly controlled during physiological circumstances [22].

According to current theories, OS is characterized by an imbalance in the formation of ROS, has a significant impact on age-related neurodegeneration & cognitive decline and anti-oxidative defence [23]. High amounts of oxidized proteins, advanced glycation products, lipid peroxidation, and the emergence of toxic chemical compounds, such as peroxides, alcohols, aldehydes, free carbonyles, ketones, and cholestenone, and also oxidative alteration in nuclear and mitochondrial DNA in neurons are all signs of increases in level of OS in AD **Fig. 4** [24].

Because the phospholipids in the CNS neuronal membrane are made up mostly of polyunsaturated fatty acids, this organ is extremely susceptible to damage from free radicals. These multiple binds allow for enhanced lipid peroxidation and hydrogen ion elimination, which is the most observable sign of degenerative change in AD [25].

Mitochondrial dysfunction & OS are connected to each other in AD. ROS will be generated as a result during mitochondrial metabolism since neurons have a high energy need for their numerous metabolic activities. As a result, mitochondrial dysfunction may cause a rise in ROS production and consequent neuronal injury [26].

Free radicals targeting phospholipid poly-unsaturated fatty acids in the phospholipid bilayer can induce oxidative stress, which can occur in peroxidation of lipid and the production of critical end products [27].

The inner mitochondrial membrane holds the mitochondrial respiratory chain. It is made up of 5 complexes that's are - I, II, III, IV, and V **Table 2** [28], which, as a part of an integrated system made up of five protein complexes, catalyse the conversion of adenosine diphosphate to adenosine triphosphate [29].

TABLE 2: MITOCHONDRIAL COMPLEXES

S. no.	Complex Name
1.	Complex I- Nicotinamide Adenine dinucleotide Dehydrogenase-Ubiquinone Reductase (coenzyme Q)
2.	Complex II- Succinate Dehydrogenase (FADH2)-coenzyme Q
3.	Complex III- Ubiquinone-cytochrome C reductase
4.	Complex IV- Cytochrome C oxidase
5.	Complex V- Adenosine triphosphate synthase

When neuronal loss and other AD disorders cause inflammation, it initially acts as an immediate neuroprotective response; but, if the immune response continues, it becomes damaging and worsens the condition. The balance between anti & pro-inflammatory signaling is disturbed by activated microglia, which then release a number of damaging substances such cytokines (interleukins (IL) and tumour necrosis factors (TNF- α) & ROS [30]. Persistent neuroinflammation is thought to worsen amyloid and tau disorders. Cytokines, specifically IL-6, are thought t promote tau hyperphosphorylation by activating protein kinases. Moreover, IL-1 increases acetylcholinesterase (Ach E) expression and activity, resulting in *in-vivo* cholinergic dysfunction studies and cholinergic neuron death [31].

FXR (Farnesoid X Receptor) PATHWAY: The liver, colon, and kidney all have high levels of the FXR, a nuclear hormone receptor super family member that functions as ligand-activated transcription factors. But little is understood about the function of the FXR in the brain [32], that controls the transcription of several genes, along with the phosphorylation of nuclear factor kappa B (NF-kB) & AMP-activated protein kinase alpha (AMPKα) [33]. In the resting state, the combination of Kelch like ECH-associated protein 1 (Keap1) (master transcription factor) and Nrf2 sequesters the protein in the cytoplasm [34, 35]. Nrf2 enters the nucleus by altering Keap1's conformation. Controls a number of anti-oxidative genes by forms a complex to the anti-oxidative response elements (ARE) in a heterodimer with the tiny Maf protein, along with hemeoxygenase - 1, xenobiotic - metabolizing enzyme to protect neuronal cells against OS [36, 37].

CONCLUSION: Two important transcription factors that are expressed in the CNS are Nrf2 and FXR. Specifically, the liver, gut, and kidney produce FXR, but recent studies have also shown its expression in the brain. FXR activation has been shown to regulate lipid& glucose metabolism, inflammation, and associated OS in the brain.

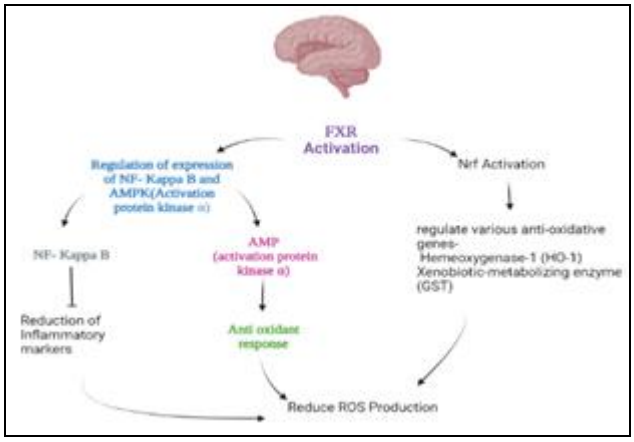

FIG. 5: POSSIBLE FXR PATHWAY

The cellular defence against oxidative stress is crucially regulated by the Nrf2 transcription factor, however, which controls the various antioxidant genes expression in body. Nrf2 activation also has been shown to provide neuroprotection by reducing ROS induced damage in the CNS. Studies have suggested a potential interaction between FXR and Nrf2 in the brain. There may be a connection between the FXR and Nrf2-mediated antioxidant response as evidenced by the finding that activation of the FXR regulates the expression of Nrf2 and its associated genes expression in the liver.

Additionally, studies have shown that activation of Nrf2can regulate FXR expression and activity in the liver, suggesting a reciprocal relationship between these two transcription factors. Although the precise link between

Nrf2 and FXR in the brain is unknown, it is probable that comparable interactions take place in this context **Fig. 5**. Overall, the activation of FXR and Nrf2 pathways may have synergistic effects on reducing oxidative stress and inflammation in the brain, making them potential therapeutic targets for neurological diseases like AD (oxidative stress induced by ROS and inflammation).

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