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Navigating the complexities: Oxidative stress and neuroinflammation in Alzheimer

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Abstract

Alzheimer's is a brain degenerative disorder distinguished by dementia, loss of memory, loss of motor skills and language, followed by difficulties in recalling recent events, conversations, or newly learned information. The impact of reduced glutathione levels in nerve cells pitches into the building of oxidative stress in the brain, thereby resulting in molecular apoptosis as well as the lipid peroxidation process. The significant amount of oxidative damage found in the brain of Alzheimer's patients is connected to abnormal Aβ plague formation and deposition regarding neurofibrillary tangles. Furthermore, this article includes the salient features of neuroinflammation in Alzheimer's disease which show chronic and self-sustaining forms of sensitivity in a micro-environment specified by tubulin binding protein, neuritic plaques, activated neuroglial cells, stressed nerve cells, also various erythrogenic chemokines and interleukins; hence, resulting in neuronal loss and intellectual disability. This review comprehensively explores the interplay between oxidative stress and neuroinflammation in AD, focusing on their molecular mechanisms, biomarkers, and potential therapeutic targets. Understanding these intricate pathways is crucial for developing effective strategies to diagnose, prevent, and treat AD, thereby improving the quality of life for affected individuals.

1. Introduction

We have taken a comprehensive approach to explore the different aspects of Alzheimer's disease (AD), including pathological, social, and therapeutic aspects. Our goal is to provide readers with a fundamental understanding of the disease, encompassing all the mentioned domains.

Alzheimer's disease is a type of brain disorder that cannot be cured. It affects the system which leads to a gradual decline in memory, cognitive abilities and the capacity to carry out basic tasks (Sonkusare *et al*., 2005). This is the leading cause of dementia, which has been affecting more than 6.5 million individuals and populations, in the United States (Abeysinghe *et al.,* 2020).

1.1 How does Alzheimer's disease affect the brain?

1.1.1 Functionally

The initial impact on the hippocampus, the amygdala, which is responsible for emotions, is subsequently affected in Alzheimer's disease (Coupé *et al.,* 2019). The amygdala is a significant player in various aspects of emotional learning and behaviour, playing a crucial role in mediating these processes.

1.1.2 Structurally

The characteristic ridges of the brain, known as gyri, gradually become narrower in Alzheimer's disease. As a result, the grooves between the gyri, called sulci, widen. This process of atrophy also leads to the enlargement of the ventricles, which are fluid-filled cavities within the brain (Avila *et al*., 2022).

2. Insights into AD progression: Signs and symptoms

Stage 1

Individuals may seem sound. There are hidden pathological transformations happening in their brain.

Stage 2

Individuals may experience mild memory loss, although it might be indistinguishable from normal forgetfulness.

Stage 3

Individuals enter a phase of mild cognitive impairment (MCI). They may encounter difficulties in finding the right words or getting lost.

Stage 4

Characterized as moderate dementia, individuals start to have poor short-term memory. They may also begin to forget some aspects of their personal history.

Stage 5

Cognition continues, and individuals require assistance in their daily lives. Confusion becomes more prominent, and they start to forget many personal details.

Stage 6

Individuals experience severe dementia and need constant supervision and care. They may no longer recognize family and friends, and there can be noticeable changes in their personality.

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Stage 7

They experience challenges find it hard to communicate face issues, with bladder and bowel control and need help with eating (Huang *et al*., 2019).

3. Decoding causes and risk factors of AD

- **Certain genetic factors:** These genes have various functions that contribute to the development of amyloid plaques and protein aggregation, two significant factors associated with this condition (Khan, 2016).
- **Life style:** Several factors related to how we live our lives have great impact on the onset of Alzheimer's disease. These factors include not being physically active having a diet, smoking drinking much alcohol and dealing with chronic stress (Huang *et al*., 2019).
- **Environmental factors:** There is evidence to suggest that being exposed to toxins or pollutants could raise the likelihood of developing Alzheimer's disease. Continuous exposure, to air pollution, heavy metals, like lead or aluminum pesticides and certain industrial chemicals might contribute to this risk (Huang *et al*., 2019).
- **Age:** After reaching the age of 65, the chances of developing this condition significantly increase (Khan, 2016).
- **Head injuries:** Repeated concussions has been found to have a connection, with a likelihood of developing Alzheimer's disease later in life (Huang *et al*., 2019).
- **Cardiovascular health:** Having bad cardiovascular health can contribute to the development of Alzheimer's disease.
- **Certain genes:** Some genes, such as the APOE gene, are associated with an increased risk of Alzheimer's disease.
- **Lifestyle factors:** Smoking and not engaging in exercise have been identified as potential factors that could increase the chances of developing Alzheimer's disease (Khan, 2016).
- **Other:** Conditions such as high blood pressure, elevated cholesterol levels, diabetes, obesity and heart disease have all been associated with a risk.

4. Pathogenesis of Alzheimer's disease

The marking symptoms of the disease are the accumulation of amyloid beta plaques and neurofibrillary tangles in the brain (Newcombe *et al*., 2018). Genetic variations in certain genes like amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) have been linked to a higher risk of developing Alzheimer's disease.

Oxidative stress and neuroinflammation play a role in the development and progression of Alzheimer's disease. Oxidative stress refers to an imbalance of oxygen species (ROS) and the body's ability to repair or prevent the resulting damage. It leads to heightened stress levels, which can cause damage to proteins, lipids and DNA due, to ROS levels (Sultana *et al*., 2010). Neuroinflammation on the other hand pertains to the activation of cells, within the brain, microglia and astrocytes. These cells release biomolecules called cytokines and chemokines that possess properties. In the context of Alzheimer's disease, neuroinflammation. It deteriorates all the neurons and contributes to the formation of amyloid beta plaques and neurofibrillary tangles (Front. Mol. Neurosci, 2017).

4.1 Oxidative stress

Oxidative stress is the process that increases in the brain as we age and occurs when there is an imbalance. This imbalance can result from the extra production of oxygen species (ROS) or a malfunctioning antioxidant system (Andreyev *et al*., 2005). The primary sources of production potentially come from mitochondria within cells and inflammation outside of cells (Ozkul *et al*., 2007). Researchers believe that mitochondrial dysfunction has an impact in degeneration of neurons in AD through ROS generation, activation of permeability transition, excitotoxicity, impaired ATP production and disrupted calcium balance.

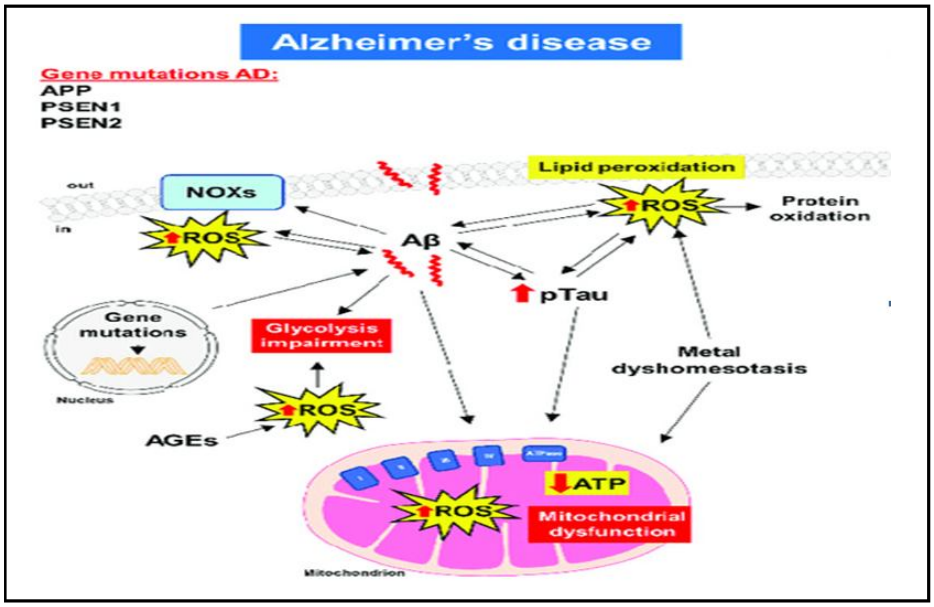

Figure 1: Pathophysiology of Alzheimer's disease by oxidative stress.

The superoxide radicals ($O_2^{\bullet -}$), radical hydrogen peroxide (H_2O_2) and hypochlorous acid molecules can cause tissue damage when excessive amounts are produced. Also due to the presence of iron or copper ions, they can form reactive hydroxyl radicals (OH•) and other oxidant molecules (Leeuwenburgh *et al.*, 2001). Furthermore, oxidative stress and neuroinflammation disrupt the self-pathways for maintaining the balance between amyloid-beta (Aβ) synthesis and degradation. There is a link between oxidative stress (OS) and Aβ as Aβ induces OS both *in vivo* and, *in vitro*. In turn, OS promotes increased production of Aβ (Alam *et al*., 2017).

4.1.1 Physiology of oxidative stress in AD

Due to the high rate of oxidative stress, the brain is particularly vulnerable to oxidative injury, which causes cellular damage, comparatively large concentration of redox transition metal ions, mitochondrial dysfunction, and inflammation besides, the brain has very low antioxidant levels (Butterfield *et al*., 2001). In fact, the build-up of Aβ protein brought on by ROS in AD results in lysosome membrane breakdown and then it leads to brain death as shown in Figure 1 (Zhang *et al.,* 2009).

a. Cellular damage by oxidative stress: Generally, the toxic effects of ROS in the cell include; which have the ability to cause harm to DNA, lipids and enzymes found within the cytoplasm of cells.

I. Lipid peroxidation of polyunsaturated fatty acids (such as membrane phospholipids).

II. Oxidation of proteins.

III. Damage on DNA or RNA; and

IV. Oxidation of sugars, glycoproteins or glycolipids (Zhang *et al.,* 2009).

b. Lipid oxidation in Alzheimer's disease: Amyloid β induces lipo-peroxidation of membranes and lipid peroxidation products (Sayre *et al*., 1997) ROS modifies lipids and strongly correlates with antioxidant enzymes, lipid peroxides, NFTs and amyloid plaques in Alzheimer's disease brains (Lovell *et al.*, 2007).

The by-products like 4-hydroxy-nonenal (HNE) F2 iso-prostanes, malondi-aldehyde and acrolein (Arlt *et al.*, 2002). 4-hydroxy-nonenal having the capacity to change proteins resulting in effects such as inhibiting glutamate and glucose transporters inhibiting the Na-K ATPases activating kinases and disrupting intracellular calcium signaling. Eventually these effects trigger a mechanism that leads to cell death through apoptosis (Mattson *et al*., 2003).

c. Protein oxidation in AD: The protein oxidation reaction results in the addition of hydroxyl groups, or protein-derived carbonyl groups. Protein-based carbonyl groups are introduced by conversion of hydroxyl groups, to ketones/aldehydes on amino acids residue. Assessing protein carbonylation serves as a means to gauge the extent of protein damage associated with conditions such, as ageing, oxidative stress, physiological disorders and Alzheimer's disease (Korolainen *et al*., 2007).

d. DNA oxidation in AD: In Alzheimer's disease it has been observed that the presence of oxygen species (ROS), in the brain causes an influx of calcium through glutamate receptors, which in turn triggers a harmful response leading to cell death (Mattson *et al*., 2003). Oxidative stress can damage DNA bases through processes such as hydroxylation, protein carbonylation and nitration (Lovell *et al.,* 2007). The generation of ROS occurs when oxygen reacts, with redox-active metals. Elevated levels of 8 hydroxy-guanosine (8OH D) and 8- hydroxy 2-deoxyguanosine (8OHD g) indicate oxidation of DNA and RNA. These markers have also been observed in the NFT and Aβ bands (White *et al*., 2006).

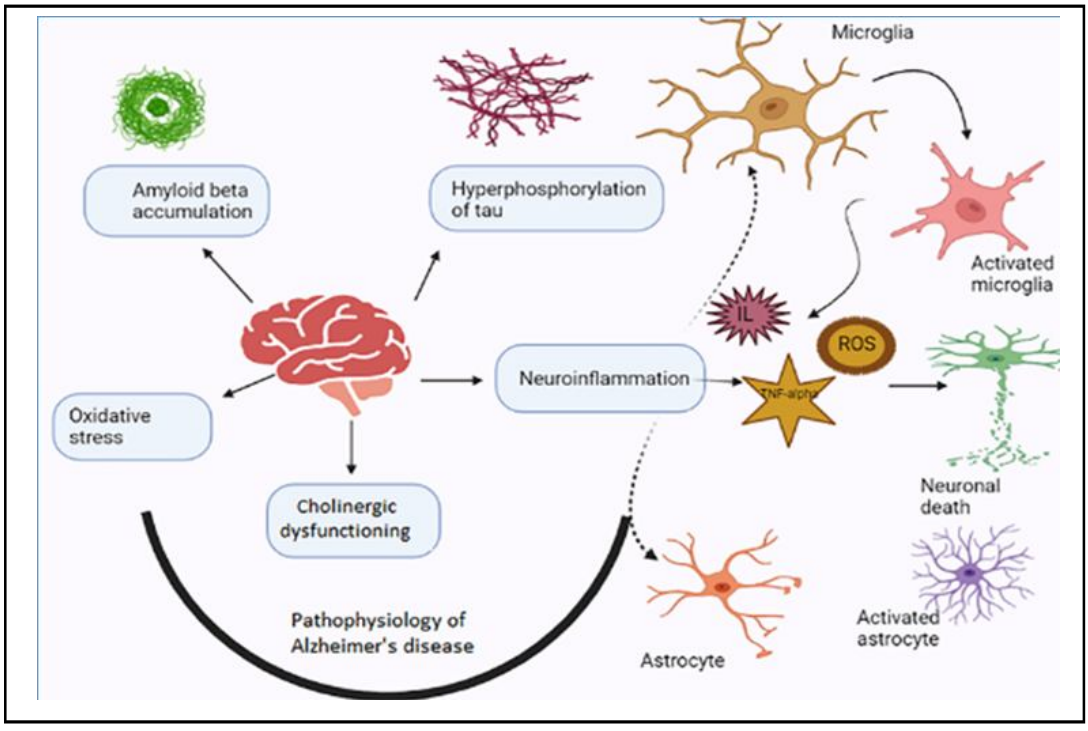

Figure 2: Pathophysiology of Alzheimer's disease by neuroinflammation.

e. **Glycoxidation in AD:** The glycation process of proteins begins when the ketone/aldehyde groups of sugars react with free-forming amino acid groups of proteins. This resulted in the formation of a Schiff base, which was first described by Maillard in 1912. Subsequent reactions lead to the creation of AGEs which are a collection of protein aggregates that are irreversibly cross-linked. The insolubility of Aβ plaques has been linked to covalent protein cross-linking, possibly facilitated by AGEs. In Alzheimer's, AGEs are formed due to the rapid oxidation of glycated proteins called "glycoxidation." Microtubule-associated protein tau (MAP tau), a factor, has been reported to induce AGEs in tangles (NFTs) in cells.

f. **Mitochondrial dysfunction:** Mitochondria are highly vulnerable, to stress due to their role in the electron transport chain, which is responsible, for producing adenosine triphosphate (ATP) and generating reactive oxygen species (ROS) (Grivennikova *et al*., 2006). Mitochondrial dysfunction and resultant metabolic abnormalities have been seen in the neurons of the hippocampus, in patients having Alzheimer's disease (Silva *et al.,* 2012).

g. **The role of metals in AD:** Metals have an impact, on the production of free radicals and there has been a focus on understanding the role of various metals, such as iron, aluminum, mercury, copper and zinc in relation to AD. The iron is particularly involved in the creation of the harmful hydroxyl radical. The possibility of copper playing a role in AD is supported by evidence showing that copper can act as a catalyst for oxygen species (ROS) production and, by data suggesting that the APP molecule contains a site where copper can bind. In human's zinc has been found to contribute to the formation of amyloid deposits. This phenomenon is not observed in rats, which may explain why cerebral beta-amyloid is scarce in these animals.

4.2 Neuroinflammation

a. The Amyloid cascade

The development of Alzheimer's disease creates amyloid plaques and neurofibrillary tangles, in the brain (Pospich *et al.,* 2017) which may result from abnormal protein processing, interfere with intracellular calcium homeostasis, free radicals, and cause neurotoxicity and plaque-associated neuronal injury. In a brain, the cell membrane of a neuron typically contains a molecule called amyloid precursor protein (APP). This protein is divided into two parts, with one end inside the cell and the other outside. APP plays a part in aiding the growth and recovery of neurons after sustaining any form of damage. The breakdown of beta amyloid, with the help of apolipoprotein E(APOE) assists, in this degradation process. Amyloid beta tends to misfold and becomes adhesive, eventually aggregating to form oligomers. These small units gradually come together to form threads that eventually settle in the brain as plaques. These aggregated forms of Aβ are insoluble and form the core of amyloid plaques. This disrupts communication between neurons.

The amyloid plaques cause inflammation; such increased chronic inflammation can further harm neurons and promote the development of the disease. Amyloid plaques can also develop around the blood vessels, in the brain a condition called amyloid angiopathy. This occurrence weakens the walls of blood vessels raising the chances of hemorrhage or rupture ultimately resulting in blood loss.

b. The Tau protein hypothesis

The buildup of tangles, in the brain are a feature of Alzheimer's disease. The tau protein is responsible for stabilizing these microtubules and preventing them from breaking apart. Just like amyloid beta, tau exists in different forms. Some forms remain soluble, while others clump together and form tangles known as neurofibrillary tangles. The abnormal modifications involve the addition of phosphate groups to the tau protein (Xu *et al*., 2014). The aggregated and hyperphosphorylated tau proteins start to accumulate within the neuronal cell body and dendrites. Over time these collections gradually come together to create strands known as paired filaments (PHFs) and straight filaments (SFs) which make up the primary elements of NFTs.

c. Microglia activation

Microglia play a role, in the brain's system acting as an integral component (Plescher *et al*., 2018). These are the CNS's immune cells (Norris *et al.,* 2019). They are initially formed in the yolk sac. Then migrate to the developing brain, where they mature into functional microglial cells (Franco *et al*., 2019).

Alterations in the appearance of microglia have been noticed in laboratory mice models with AD. With age, changes occur in microglia. Create an active environment that produces pro inflammatory cytokines such as IL 1β, TNFα and IL6 (Tejera *et al.,* 2016). It is believed that Aβ triggers the activation of microglia, which subsequently releases IL1β IL6 and TNFα, along with ligands such as CCL2/4/11. This leads to the attraction of microglia and astrocytes, to the amyloid beta site (Koenigsknecht *et al.,* 2005). First, microglia activation may have a role, in removing Aβ and result in neurotoxicity, moreover, it also indicates a rise, in the generation of inflammatory substances, like reactive oxygen species (ROS) and cytokines (Tuppo *et al.,* 2005).

d. Astrocyte activation

Astrocytes play a role in the release of important substances, including neurotransmitters, like glutamate, GABA and ATP. They also release neuromodulators such as de serine and kynurenic acid, as well as growth factors and inflammatory mediators. Astroglia are found on the surface of the central nervous system (CNS) and are considered the most abundant cells in the brain (Colton *et al.,* 2006). When astrocytes are linked to plaques, they undergo changes, in their shape and size characterized by branches and an increase in the production of specific proteins, for example, glial fibrillar acidic protein (GFAP) vimentin, nestin, and cinamin (Malarkey *et al.,* 2008). In addition, when astrocytes undergo a reactive state, they increase the levels of sAPP-α and the enzyme responsible for cleaving APP at the Aβ site, known as BACE1. This upregulation ultimately results in the formation of Aβ.

5. Diagnosis

In Alzheimer's disease (AD), various biomarkers are utilized for diagnosing and monitoring the progression of the disease. These biomarkers can be broadly classified into imaging biomarkers, cerebrospinal fluid (CSF) biomarkers, and blood-based biomarkers.

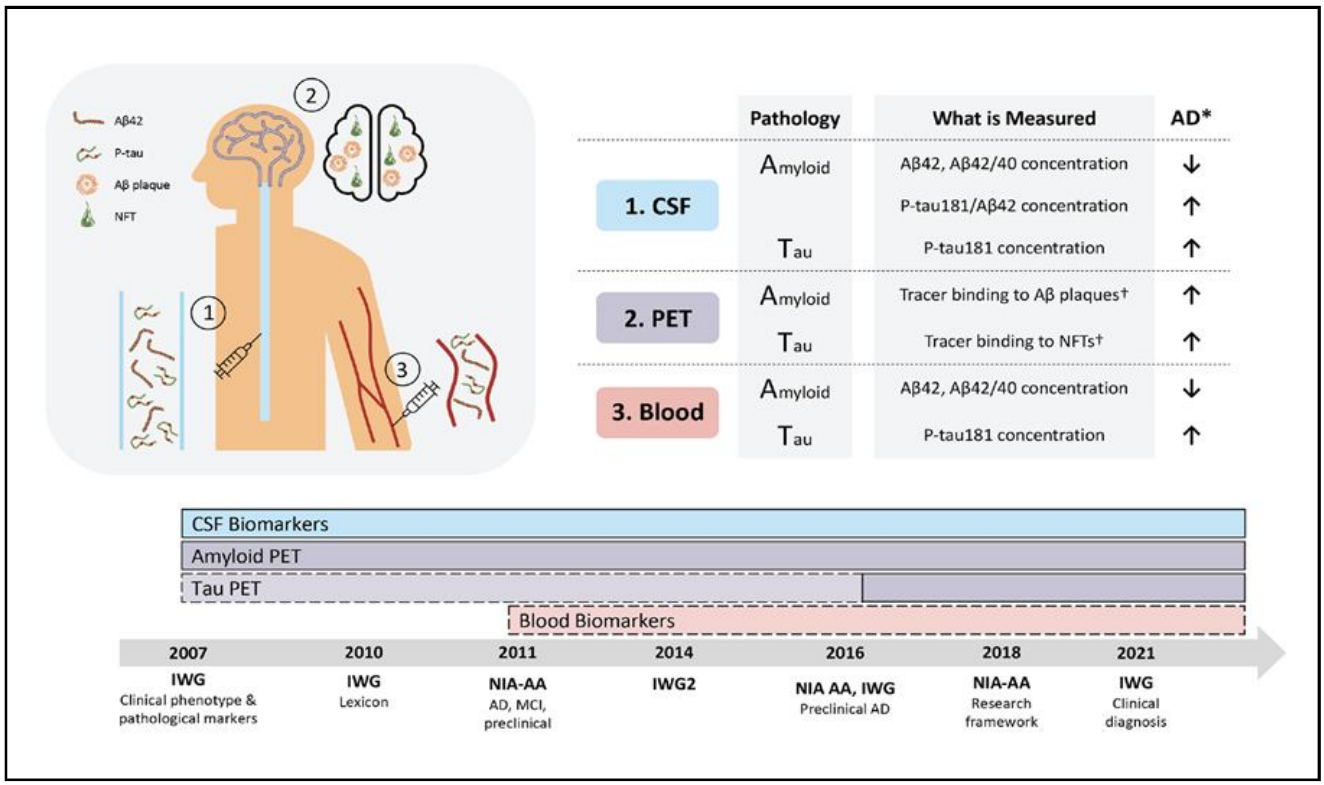

Figure 3: Diagnostic biomarkers in Alzheimer's disease.

5.1 Brain imaging

5.1.1 Magnetic resonance imaging (MRI)

MRI in diagnosing Alzheimer's disease is to measure changes, in volume at locations, which can provide diagnostic accuracy of up to 87% (Pekny *et al*., 2016). The diagnosis should be determined by considering two characteristics

1. Atrophy, in the lobe specifically affecting the hippocampus, entorhinal cortex and perirhinal cortex.
2. Atrophy, in the cortex

On average they tend to lose twice much brain volume per year (around 1% compared to approximately 0.5%). The impact is particularly significant in the hippocampi, where those affected can experience three times the amount of volume loss per year (4.5% compared to, around 1.5%) (Escartin *et al.,* 2021).

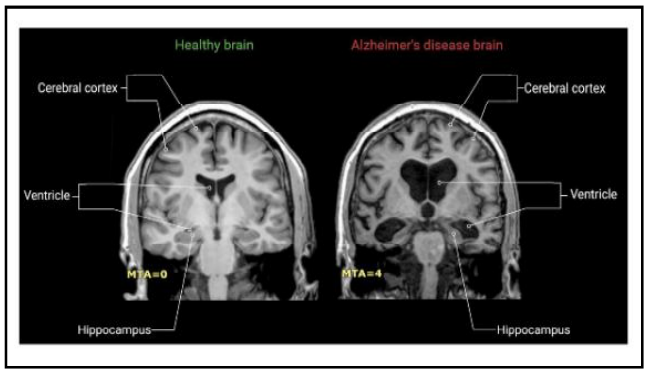

Figure 4: MRI scan of a healthy brain and Alzheimer's brain.

5.1.2 Diffusion tensor imaging

Diffusion tensor imaging (DTI), a method of brain imaging that utilizes the characteristics of water molecules diffusion to produce MRI reflecting alterations, in the organization of nerve fibers. This technique enables the assessment of micro circuits known as "mini columns" (Miller-Thomas *et al.,* 2016).

5.1.3 PET Scan

Two types of proteins amyloid β (Aβ). Hyper phosphorylated tau protein builds up in the brains of individuals, with Alzheimer's disease (AD). PET scans have the ability to evaluate both proteins and act as biomarker in AD.

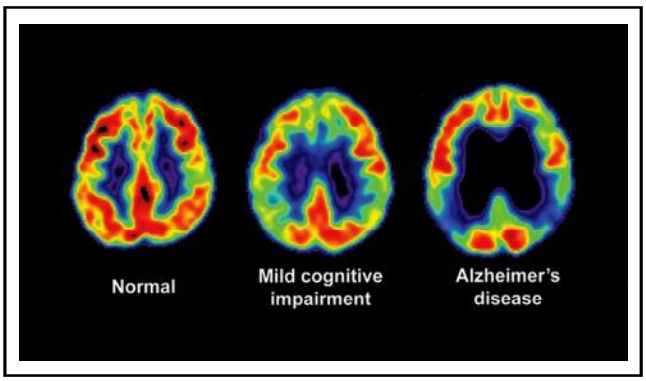

Figure 5: PET Scan of normal and Alzheimer diseased brain.

5.2 CSF and blood tests

Fluid (CSF) which surrounds the brain and can be accessed through a lumbar puncture undergoes changes, in the levels of Aβ and tau

proteins before clinically significant in Alzheimer's disease (AD) symptoms appear. In decades' various tests have been developed to analyze CSF. The notable ones include examining the ratio of CSF Aβ 42 to Aβ 40 and measuring CSF tau phosphorylated at threonine 181 (P tau181). There is hope that measuring CSF P tau 217, in the circulation could serve as a sensitive and specific biomarker (Landhuis *et al*., 2021).

6. Treatment of AD

a. Flavonoids

The drugs commonly utilized include apigenin, iso-quercitrin, morin, fisetin, quercetin, naringenin, luteolin and the mediterranean diet, which includes a variety of foods, fruits, vegetables and wine has shown evidence of reducing the progression of mild cognitive impairment to Alzheimer's disease. The process that operates is the restoration of the ERK/CREB/BDNF pathway in the cortex, which involves signal kinase and cAMP response element binding protein (Scarmeas *et al.,* 2018).

b. NSAID's

The use of ibuprofen, over a period of time has been linked to cognitive decline. Minocycline, a tetracycline with inflammatory properties has shown the ability to protect it against the harmful effects of Aβ in lab tests and animal models of Alzheimer's disease. However, it does not show any delay in functional decline in AD patients during a trial. Continuous activation of the system leads to the release of pro-inflammatory cytokines and harmful substances. As a result, it might be worth considering inflammatory medications as potential treatments for Alzheimer's disease as well (Shishtar *et al*., 2020).

c. Antioxidants

Antioxidants, such, as vitamin C, E, B12, CoQ10, caffeine, silibinin and others. They play a crucial role in reducing the damaging impact of oxidative stress. They effectively mitigate the occurrence of stress, at lower concentrations. The primary function of antioxidants is to neutralize radicals and impede the chain reaction that leads to stress (Gyengesi *et al*., 2020).

d. Nutraceuticals

EGb 761 an extract derived from *Ginkgo biloba* is commonly used to treat disorders, like AD. It has shown benefits in enhancing function reducing neuropsychiatric symptoms and improving daily activities in individuals with mild, to moderate dementia. Curcumin, known for its antioxidant properties and anti-inflammatory properties can effectively cross the BBB. Studies have suggested that it can inhibit glycogen synthase kinase 3β (GSK 3β) and CDK5 activities (Pritam *et al*. 2022).

e. Anti-Tau DMTs

Phosphatase activation and hyperphos-phorylated tau aggregates are implicated in the neurotoxicity discovered in AD brain. There has been some potential demonstrated for methylene blue dye derivatives in their ability to block the formation of tau aggregates. Methylene blue has several beneficial properties, such as interrupting tau aggregation, preventing amyloid aggregation, decreasing oxidative stress, guarding against mitochondrial damage, and modifying autophagy.

7. Discussion

The pathological impact of Alzheimer's disease is profound and multifaceted, affecting both brain structure and function. AD initially targets key regions like the hippocampus and amygdala, disrupting memory and emotional processing, respectively. As the disease progresses, noticeable brain changes such as the atrophy of gyri and widening of sulci become apparent, reflecting the degenerative nature of AD. Understanding AD's progression is crucial for caregivers and healthcare professionals. The delineation of stages, from subtle cognitive changes to severe dementia, provides a roadmap of the challenges individuals with AD face. This knowledge not only aids in early detection but also guides interventions and support strategies tailored to each stage. The causes and risk factors of AD are diverse, encompassing genetic predispositions, lifestyle choices, environmental influences, age-related factors, head injuries, and cardiovascular health. This comprehensive view underscores the complex interplay of genetic and environmental factors in AD's etiology, highlighting the importance of personalized risk assessment and preventive measures. The pathogenesis of AD involves intricate molecular mechanisms such as amyloid beta plaques, neurofibrillary tangles, oxidative stress, and neuroinflammation. These processes link genetic variations to protein aggregation and cellular damage, bridging the gap between molecular events and clinical symptoms. Understanding these mechanisms is crucial for developing targeted therapies and interventions.

8. Conclusion

The review articles and studies mentioned provide a comprehensive overview of the role of oxidative stress and neuroinflammation in Alzheimer's disease. They highlight the intricate relationship between these factors and the pathophysiological mechanisms underlying the development and progression of the disease. From these discussions, it can be concluded that oxidative stress and neuroinflammation play crucial roles in Alzheimer's disease contributing to the neurodegenerative processes and cognitive impairment observed in affected individuals. Targeting these pathways may hold promise for developing therapeutic interventions aimed at slowing down or halting the progression of Alzheimer's disease.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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