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Review

Understanding Alzheimer's Disease: A Comprehensive Review

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Abstract

Alzheimer's disease (AD) is a progressive neurological disorder and the leading cause of dementia in the elderly. It is distinguished by memory loss, cognitive deterioration, and personality shifts. Despite substantial research, the pathophysiology of Alzheimer's disease is not fully understood, and viable treatments are missing. This review seeks to offer a complete overview of current AD knowledge, including epidemiology, pathophysiology, genetic and environmental risk factors, diagnostic criteria, and therapeutic approaches.

Keywords: Alzheimer's disease (AD), Dementia, Amyloid-beta plaques, Neuro fibrillary tangles, Tau protein, Neuro inflammation, Cognitive decline, biomarkers, Monoclonal antibodies.

INTRODUCTION

Alzheimer's disease is a huge public health concern with serious social and economic consequences. The condition is distinguished by a steady decline in cognitive abilities such as memory, thinking, language, and the capacity to perform daily tasks. In addition to cognitive impairment, people with Alzheimer's disease frequently have behavioral and psychological symptoms such depression, anxiety, agitation, and psychosis. It is estimated that more than 50 million people worldwide suffer from dementia, with Alzheimer's disease accounting for roughly 60-70% of these instances. The incidence of Alzheimer's disease rises with age, and as the world population ages, the prevalence of AD is predicted to climb significantly in the future decades. This review summarizes the most recent studies on Alzheimer's disease, emphasizing breakthroughs in our understanding of its origin, development, and treatment.

Epidemiology

AD primarily affects people over the age of 65, and the risk doubles every five years after that age. Women are disproportionately affected, owing to their longer life expectancy. The disease burden varies by area, with increased prevalence in high-income countries, most likely due to longer life expectancy and improved diagnostic capabilities. Early-onset Alzheimer's disease, which begins before the age of 65, accounts for less than

5% of cases and is frequently associated with genetic changes. AD has a global frequency of around 24 million cases, which is anticipated to quadruple every 20 years, reaching more than 80 million by 2040. The expense of controlling AD is enormous, with projections indicating that the global cost of dementia would approach $1 trillion by 2030. These findings highlight the critical need for better prevention and treatment techniques.

Pathophysiology

- Alzheimer's disease is characterized by the formation of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) in the brain, which are made up of hyperphosphorylated tau proteins. These pathogenic alterations are associated with neuronal loss, synaptic dysfunction, and gliosis.
- Amyloid Beta Pathway: According to the amyloid hypothesis, Alzheimer's disease is primarily caused by the overproduction and buildup of Aβ peptides, which are produced from the amyloid precursor protein (APP) through successive cleavage by β-secretase and γ-secretase (Hardy & Selkoe, 2002). Aggregated Aβ produces plaques that impede cell-to-cell communication and activate immunological responses, resulting in persistent inflammation and neuronal death.
- Genetic mutations in APP and presenilins (PSEN1 and PSEN2) can lead to family types of Alzheimer's disease, confirming the amyloid hypothesis (Hardy & Higgins, 1992). The exact mechanism of Aβ's contribution to neuro degeneration is currently being disputed. According to Haass and Selkoe (2007), soluble Aβ oligomers may be more hazardous than insoluble fibrillar plaques, affecting synaptic function and plasticity.
- Tau Pathway: NFTs are formed when tau protein, which keeps neuronal microtubules stable, is hyperphosphorylated in AD. These tangles cause axonal transport to be hampered and contribute to cell death by interfering with microtubule activity (Goedert et al., 2017). According to the tau hypothesis, tau disease results from Aβ accumulation, however there is also data that implies tau may be the fundamental cause of neurodegeneration (Iqbal et al., 2010).
- According to Braak & Braak (1991), tau pathology can begin independently of Aβ in animal models, and its progression is more closely correlated with clinical symptoms and neuronal death than Aβ plaque load. This has given rise to the dual route hypothesis, which postulates that tau and Aβ both independently and cooperatively propel the course of the disease.Tau Route
- Neuro inflammation: An increasingly important role for neuro inflammation in AD etiology is being acknowledged. According to Heneka et al. (2015), activated microglia and astrocytes intensify neuronal injury by releasing pro-inflammatory cytokines and reactive oxygen species. According to Guerreiro et al. (2013), genetic research has revealed the presence of multiple immune-related genes, including TREM2, that impact the risk of AD. These findings highlight the critical role that the immune response plays in advancing the disease.
- The development of AD may be aided by chronic neuro inflammation, which can set off a self-sustaining cycle of inflammation and neuronal damage. As the brain's native immune cells, microglia may both remove injured neurons and Aβ, but they can also become overactive and produce neurotoxicity in AD. In addition to supporting neuronal function and preserving the blood-brain barrier, astrocytes can become reactive and fuel neuroinflammation (Leng & Edison, 2021).

Genetic and Environmental Risk Factors

Genetic Factors

In AD, genetic predisposition is a major factor. The largest genetic risk factor for late-onset AD is the ε4 allele of the apolipoprotein E (APOE) gene, which lowers the age of onset and increases risk (Corder et al., 1993). AD pathogenesis is exacerbated by APOE ε4 carriers' increased Aβ accumulation and poor Aβ clearance (Kim et al., 2009). Mutations in the APP, presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes are associated with familial AD, which makes up a tiny portion of patients (Rogaeva et al., 2001). Early-onset AD, which usually manifests before the age of 65, is caused by these mutations that result in increased production or impaired clearance of Aβ.

According to Lambert et al. (2013), genome-wide association studies (GWAS) have discovered more risk loci linked to AD, such as those related to inflammation (CR1, TREM2), lipid metabolism (CLU, ABCA7), and endosomal vesicle recycling (PICALM). These results emphasize how intricately genetic variables interact in AD. A vital hormone for women, estrogen has been thoroughly researched for its neuroprotective properties, especially in relation to Alzheimer's disease (AD). Numerous processes, such as altered synaptic plasticity, decreased oxidative stress, and improved mitochondrial function, are involved in estrogen's effects on the brain.

Mechanisms of Estrogen Synaptic Plasticity and Neurotransmission That Protect the Neurons: It has been demonstrated that estrogen increases synaptic plasticity, which is essential for memory and learning. It regulates neurotransmitter production and absorption, particularly acetylcholine, which is profoundly impacted in

AD. The hippocampus and cerebral cortex are two important brain areas involved in cognition that are home to estrogen receptors (ERα and ERβ), suggesting that estrogen directly affects cognitive function (Brinton, 2009).

Oxidative Stress and Inflammation

of the main factors in the pathophysiology of AD is oxidative stress, which estrogen helps to lower thanks to its antioxidant qualities. It increases the expression of antioxidant enzymes and suppresses the generation of reactive oxygen species (ROS). Furthermore, microglia activation and the release of pro-inflammatory cytokines, which are linked to neurodegeneration, are decreased by estrogen's anti-inflammatory properties (Yao et al., 2010).

Mitochondrial Function

By encouraging ATP synthesis and lowering ROS in the mitochondria, estrogen improves mitochondrial function. Given that mitochondrial failure is a common aspect of AD, this effect is crucial. Enhancing mitochondrial function contributes to apoptosis prevention and neuronal health maintenance (Simpkins et al., 2005).

Estrogen and Risk of Alzheimer's Disease

Studies on epidemiology point to a connection between estrogen levels and AD risk. Compared to men, women are more likely to develop AD, especially after menopause when estrogen levels start to drastically drop. One possible tactic to lower the risk of AD has been studied: hormone replacement treatment (HRT). According to some research, HRT can help lower the risk of AD or postpone its onset, particularly when it is started around menopause (Wang et al., 2000). The type and timing of hormone therapy, however, are very important because starting HRT later in life may not have the same advantages and may even raise the risk of cognitive decline. Research on the possible therapeutic benefits of selective estrogen receptor modulators (SERMs) and estrogen in AD is ongoing. Serum estrogen receptor modulators (SERMs), such raloxifene, replicate the positive effects of estrogen in the brain without posing the same hazards to other organs including the breast and uterus. According to Smith et al. (2017), clinical trials are being conducted to assess the effectiveness of SERMs in enhancing cognitive performance and delaying the onset of AD.

Exposure to radiation from medical treatments and environmental sources has been linked to a number of health hazards, including neurodegenerative illnesses and cognitive impairment. There is a complicated correlation between radiation exposure and Alzheimer's disease that depends on a number of variables, including the kind, amount, and time of exposure.

Radiation-Induced Neurodegeneration

Oxidative Stress and Inflammation

By producing reactive oxygen species (ROS), ionizing radiation can cause oxidative stress, which can result in cellular damage and apoptosis. According to Cherry et al. (2012), oxidative stress has the ability to cause neuroinflammation, which involves the activation of astrocytes and microglia and leads to neuronal injury and cognitive loss. Since AD is characterized by chronic neuroinflammation, radiation-induced inflammation may worsen or hasten the course of the illness.

DNA Damage and Repair

Exposure to radiation can harm neurons' DNA, which can result in mutations and poorer neuronal performance. DNA damage can have a significant impact on the health and function of neurons even though they don't normally divide. Aging brains with ineffective DNA repair systems exacerbate the harmful effects of radiation, which may raise the chance of AD (Kempf et al., 2014).

Blood-Brain Barrier (BBB) Disruption

Radiation can damage the BBB, making it possible for inflammatory cells and neurotoxic chemicals to reach the brain. Because it promotes the buildup of amyloid-beta and other harmful proteins, BBB disruption is linked to the pathophysiology of AD (Mao et al., 2010).

Therapeutic Radiation

It's interesting to note that low-dose radiation therapy has been considered for AD treatment. The possibility of reducing amyloid-beta plaque load and neuroinflammation in AD models with low-dose ionizing radiation has been explored in preclinical research and early-phase clinical trials. According to cuttler and Sanders (2017), the basic theory is that low-dose radiation may cause a mild stress response that activates defense mechanisms in cells without seriously harming them. To ascertain its safety and effectiveness, radiation therapy for AD is currently in its experimental stages and needs more research.

Occupational and Environmental Exposure

Regarding the risk of AD, epidemiological research on radiation exposure from the environment and at work has produced conflicting findings. Employees in fields where radiation exposure is high, such nuclear power plants, may be more susceptible to dementia and cognitive decline. Tofilon & Fike (2000) state that further research is necessary to establish a definitive link between radiation exposure and the risk of AD, as the current evidence is inconclusive.

Elements of Environment and Lifestyle

Numerous risk variables that can be altered have been found, such as diet, physical exercise, cognitive engagement, and cardiovascular health. Increased risk of AD is linked to hypertension, diabetes, obesity, and hypercholesterolemia, most likely via vascular and metabolic pathways (Livingston et al., 2020). Diet and exercise are examples of lifestyle factors that influence AD risk. Antioxidant-rich diets, such the Mediterranean diet, along with regular exercise and mental stimulation are linked to a decreased risk of cognitive decline (Scarmeas et al., 2006). These variables may affect inflammation, vascular health, and brain plasticity, which may all have an impact on AD risk.

New research points to the importance of sleep quality as an additional component. Increased Aβ deposition and cognitive impairment have been related to sleep disruptions, including impaired slow-wave sleep (Ju et al., 2014). Therefore, treating sleep disturbances might be a modifiable target for the prevention of AD.

Diagnostic Criteria and Biomarkers

A combination of clinical assessment, cognitive testing, and neuroimaging is used to diagnose AD. The use of biomarkers to aid in diagnosis and monitor the course of disease is growing.

Clinical and Neuropsychological Evaluation

A thorough medical history, a physical examination, and cognitive testing are required for the clinical diagnosis of AD. Two widely used instruments for evaluating cognitive performance are the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) (Folstein et al., 1975; Rosen et al., 1984). Certain patterns of cognitive impairment, such as memory loss, language difficulty, and executive dysfunction, that are typical of AD can be identified by neuropsychological testing. Input from family members and caregivers who may shed light on the patient's decrease in cognition and function frequently supports the diagnosis.

Neuroimaging

Neuroimaging methods like positron emission tomography (PET) and magnetic resonance imaging (MRI) shed light on the anatomy and function of the brain. MRI can identify brain atrophy, especially in the medial temporal lobe and hippocampal regions, which are early indicators of Alzheimer's disease (Jack et al., 2011). These diseases can be seen in vivo using PET imaging with tracers that target tau (e.g., AV-1451) and Aβ (e.g., Pittsburgh Compound-B) (Johnson et al., 2016).

The brain's glucose metabolism can also be measured with fluorodeoxyglucose (FDG)-PET, another imaging technique. Alzheimer's disease (AD) can be distinguished from other dementias by its reduced glucose metabolism in the parietal and temporal lobes (Mosconi et al., 2008).

Cerebrospinal Fluid Biomarkers

Alterations in the levels of tau and Aβ linked to AD can be found through analysis of cerebrospinal fluid (CSF). AD pathology is indicated by decreased CSF Aβ42 and higher levels of phosphorylated tau (p-tau) and total tau (t-tau) (Blennow et al., 2010). Early identification and distinction from other neurodegenerative disorders can be facilitated by these biomarkers. One of the most recent developments is the creation of blood-based AD biomarkers. As non-invasive indicators of AD pathology, plasma levels of Aβ42/Aβ40 and p-tau have demonstrated promise, possibly allowing for an earlier and more easily accessible diagnosis (Janelidze et al., 2020).

Therapeutic Strategies

The current approach for treating AD is symptom control, since no disease-modifying medications are available. Ongoing research, however, attempts to create treatments that focus on the fundamental pathophysiology of AD. Pharmaceutical Interventions Memantine, an NMDA receptor antagonist, and cholinesterase inhibitors (donepezil, rivastigmine, galantamine) are the two main medication families approved for AD. Acetylcholine levels in the brain are raised by cholinesterase inhibitors, which may enhance daily

activities and cognitive performance (Birks, 2006). Memantine helps people with moderate to severe AD by regulating glutamatergic neurotransmission (McShane et al., 2019).

The development of tau and Aβ-targeting disease-modifying treatments has been the main focus of recent efforts. Interest is still high despite clinical trial disappointments. Although their therapeutic benefits are still being studied, monoclonal antibodies targeting Aβ, including aducanumab, have demonstrated promise in lowering Aβ plaques (Alexander et al., 2021). β-secretase inhibitors and tau aggregation inhibitors are two more strategies that are presently undergoing clinical trial testing (Egan et al., 2018).

Non-Pharmacological Interventions

There is growing recognition of the potential of non-pharmacological interventions to halt cognitive decline and enhance quality of life. These interventions include cognitive training, physical activity, and habit changes. Delay the onset of dementia symptoms and improve cognitive reserve are the goals of cognitive training programs (Teri et al., 2003). Groot et al. (2016) have demonstrated that physical exercise enhances vascular function and reduces inflammation, which in turn improves brain health and lowers the risk of Alzheimer's disease.

Dietary therapies, such the MIND and Mediterranean diets, are linked to a decreased risk of AD and cognitive impairment. These diets stress avoiding red meat and sweets and increasing the intake of fruits, vegetables, whole grains, nuts, and seafood (Morris et al., 2015). Antioxidants and omega-3 fatty acids are two nutritional supplements whose neuroprotective properties are currently being researched.

Emerging Therapies and Future Directions

There are a number of intriguing strategies being researched in the ongoing search for viable AD therapeutics. The creation of novel therapeutic approaches has resulted from advances in our knowledge of the molecular and cellular mechanisms underlying AD.

Immunotherapy

The goal of immunotherapy is to strengthen the immune system's ability to eliminate tau and Aβ clumps. Passive immunization entails the delivery of monoclonal antibodies, whereas active immunization procedures use vaccines that induce the development of antibodies against Aβ or tau. To assess the effectiveness and safety of these methods, clinical trials are being conducted (Sevigny et al., 2016).

Gene Therapy

With gene therapy, genetic risk factors for AD may be altered, or protective mechanisms may be strengthened. Strategies like CRISPR-Cas9 and viral vector-mediated gene transfer are being investigated to target genes that regulate neuroinflammation and metabolism of tau and Aβ.

Neuro protection

The goal of neuroprotective techniques is to strengthen brain resilience and avoid or lessen neuronal damage. Researchers are looking into drugs that may shield neurons and enhance cognitive performance by addressing oxidative stress, mitochondrial malfunction, and excitotoxicity (Contestabile et al., 2021). Another cutting-edge strategy that may help repair the brain and replace damaged neurons is stem cell therapy. Although preclinical research has yielded encouraging findings, problems with cell survival, differentiation, and integration make clinical translation difficult.

Personalized Medicine

Treatment outcomes for AD may be improved by personalized medicine strategies, which customize therapy based on a person's genetic and biomarker profiles. Personalized medicine can improve treatment efficacy and minimize adverse effects by identifying patients who are most likely to benefit from particular medications (Nikolich-Žugich & Goldman, 2020).

Collaborative Efforts

Accelerating the translation of research discoveries into clinical practice requires more collaboration amongst regulatory agencies, industry, and academia. Our understanding of AD and the development of new therapeutics are greatly aided by public-private collaborations and large-scale research consortia like the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Dominantly Inherited Alzheimer Network (DIAN) (Weiner et al., 2017).

CONCLUSION

Alzheimer's disease continues to pose a serious threat to global healthcare systems. Even while our knowledge of the disease's pathogenesis and risk factors has advanced significantly, there are still no viable treatments that can slow the disease's progression. Ultimately, finding a cure for AD will depend on ongoing research efforts in conjunction with early diagnosis and comprehensive care plans. These measures will improve the lives of those who are impacted by the disease.

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