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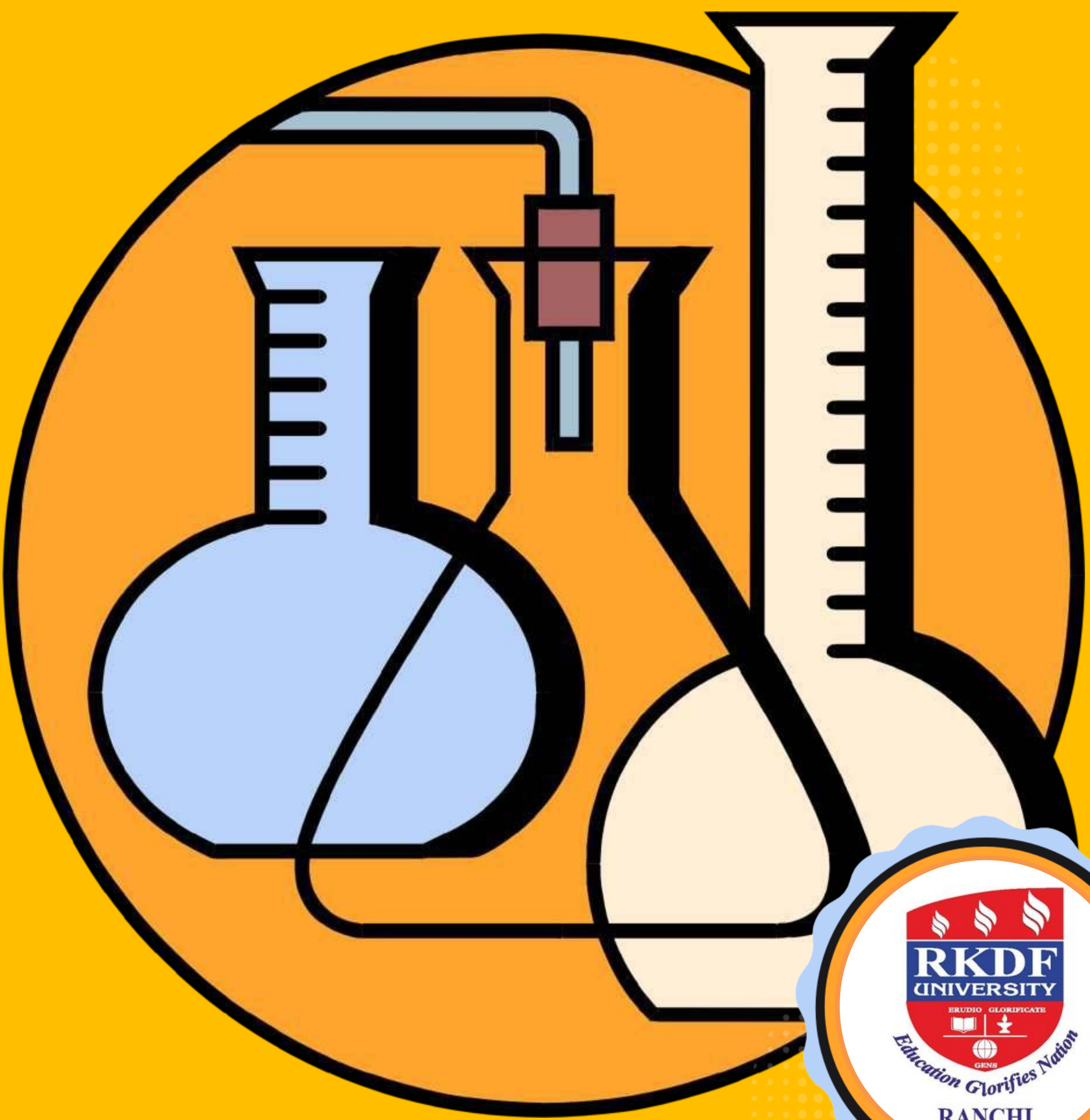

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Article: 1

Pharmacological Intervention of Alzheimer Disease

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Abstract

Several prescription drugs are approved by the U.S. Food and Drug Administration (FDA) for Alzheimer's disease to help either manage the symptoms of or to treat the disease. Most FDA-approved drugs work best for people in the early or middle stages of Alzheimer's. There are currently no known interventions that will cure Alzheimer's. Alzheimer's researchers continue to explore a variety of innovative approaches to treat symptoms as well as underlying disease processes. In ongoing clinical trials, they are developing and testing several new possible interventions. These include additional immunotherapy and other drug therapies, cognitive training, diet, and physical activity. While our era offers much more in the way of therapeutics for AD, it is clear that more work still needs to be done.

Keywords: Alzheimer's disease, Dementia, Pharmacologic Therapy

Introduction

Alzheimer disease (AD) first characterized by Alois Alzheimer in 1907 is a gradually progressive dementia affecting both cognition and behavior. Patients eventually lose cognitive, analytical, and physical functioning and the disease is ultimately fatal. AD is defined by both neuropathologic and clinical criteria. Neuropathologically AD destroys neurons in the cortex and limbic structures of the brain, particularly the basal forebrain, amygdala, hippocampus, and cerebral cortex. These areas are responsible for higher learning, memory, reasoning, behavior, and emotional control[1].

Non-pharmacologic Therapy

Sleep disturbances, wandering, urinary incontinence, agitation and aggression should be managed with behavioral interventions whenever possible. On initial diagnosis, the patient and caregiver should be educated on the course of illness, available treatments, legal decisions, changes in lifestyle that will be necessary with disease progression, and other quality of life issues. The Alzheimer's Association recommends staying physically, mentally and socially active, adopting a low-fat/low-cholesterol diet rich in dark vegetables and fruit, and managing body weight.

Managing blood pressure, cholesterol, and blood sugar may reduce the risk of developing AD and may prevent the worsening of dementia in patients with AD. Current pharmacotherapeutic interventions are primarily symptomatic attempts to improve or maintain cognition. Successful treatment reflects a decline of less than 2 points each year on the MMSE (Mini Mental Score Examination) score[2].

Pharmacologic Therapy

Cholinesterase Inhibitors such as Donepezil, rivastigmine, and galantamine are indicated in mild to moderate AD, while donepezil is also indicated in severe AD. The most frequent adverse effects are mild to moderate Gastro-intestinal symptoms (nausea, vomiting, and diarrhea), urinary incontinence, dizziness, headache, syncope, bradycardia, muscle weakness, salivation, and sweating. Abrupt discontinuation can cause worsening of cognition and behavior in some patients. Donepezil (Aricept) is a piperidine derivative with specificity for inhibition of acetylcholinesterase rather than butyrylcholinesterase. Rivastigmine has central activity at acetylcholinesterase and butyrylcholinesterase sites, but low activity at these sites in the periphery. Galantamine is a cholinesterase inhibitor that also has activity as a nicotinic receptor agonist. Tacrine was the first cholinesterase inhibitor approved for the treatment of AD, but it has been replaced by safer drugs which are better tolerated[3].

Other Drugs

Memantine (Namenda) blocks glutamatergic neurotransmission by antagonizing *N*-methyl-D -aspartate receptors, which may prevent excitotoxic reactions. It is used as monotherapy, and data suggest that when it is combined with a cholinesterase inhibitor, there is improvement in cognition and activities of daily living. It is indicated for treatment of moderate to severe AD. It is not metabolized by the liver, but is primarily excreted unchanged in the urine (half-life of elimination = 60 to 80 hours). It is usually well tolerated, and side effects include constipation, confusion, dizziness, hallucinations, headache, cough, and hypertension. It is initiated at 5 mg/day and increased weekly by 5 mg/day to the effective dose of 10 mg twice daily. Dosing must be adjusted in patients with renal impairment. Recent trials do not support the use of Estrogen to prevent or treat cognitive decline. Evidence related to the role of vitamin E in preventing AD is mixed, and conclusions cannot be drawn at this time. Because of a significant incidence of side effects and a lack of compelling evidence, non-steroidal anti-inflammatory drugs are not recommended for treatment or prevention of AD. There is interest in the use of lipid-lowering agents, especially the 3- hydroxy-3-methylglutaryl coenzyme A–reductase inhibitors, to prevent AD. Pravastatin and lovastatin, but not simvastatin, were associated with a lower prevalence of AD. Further study is needed before these agents can be recommended for this use.

Pharmacotherapy of Non-cognitive Symptoms

Pharmacotherapy is aimed at treating psychotic symptoms, inappropriate or disruptive behavior, and depression. General guidelines include use of reduced doses, monitor closely, titrate dosage slowly, document carefully and periodically attempt to reduce medication in minimally symptomatic patients.

Antipsychotics

Antipsychotic medications have traditionally been used to treat disruptive behaviors and psychosis in AD patients. A meta-analysis showed that 17% to 18% of dementia patients showed a modest treatment response to atypical antipsychotics. Adverse events included somnolence, extrapyramidal symptoms, abnormal gait, worsening cognition, cerebrovascular events, and increased risk of death. Typical antipsychotics may also be associated with a small increased risk of death, as well as more severe extrapyramidal effects and hypotension. Eg; Haloperidol, Olanzapine, Quetiapine, Risperidone, Ziprasidone

Antidepressants

Depression and dementia have many symptoms in common, and the diagnosis of depression can be difficult, especially later in the course of AD. Eg; Citalopram, Escitalopram, Fluoxetine, Paroxetine, Sertraline.

Treatment with a selective serotonin reuptake inhibitor is usually initiated in depressed patients with AD. Paroxetine causes more anticholinergic side effects than the other selective serotonin reuptake inhibitors. Venlafaxine may also be used. Although probably equally effective, the tricyclic antidepressants are usually avoided because of anticholinergic side effects[4].

Conclusion

Treating the symptoms of Alzheimer's can help provide people with comfort, dignity, and independence for a longer period of time and also assist their caregivers. A number of drugs have been approved for the treatment of Alzheimer's disease (AD) and a larger number are being studied as possible therapies. The current mainstays of the pharmacotherapy of AD are the cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine. They collectively have acceptable tolerability and proven but modest efficacy.

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Article: 2

Pathological Progression of Alzheimer Disease

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Abstract

According to Centers for Disease Control and Prevention (CDC) data, Alzheimer disease (AD) is ranked as the seventh leading cause of death in the United States in 2022, while COVID-19 ranked fourth. Before the COVID-19 pandemic, AD was the sixth leading cause of death following stroke. AD is characterized pathologically by an accumulation of abnormal neuritic plaques and neurofibrillary tangles in the brain. These pathological changes are accompanied by a loss of neurons, particularly cholinergic neurons in the basal forebrain and the neocortex. Alzheimer's disease tends to develop slowly and gradually worsens over several years.

Keywords: Alzheimer disease, Brain, Plaques, Complex Disorders

Introduction

Alzheimer's disease (AD) is an incurable, debilitating sickness that causes cognitive and behavioural deterioration over a protracted period of time. Plaques form in the cerebral cortex and other regions involved in thought and decision-making in AD, including the hippocampus, a structure located deep within the brain that aids in memory encoding. Worldwide, there are more than 55 million dementia sufferers, 60% of whom reside in low- and middle-income nations. Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia among the elderly, marked by a gradual decline in cognitive functions such as memory, reasoning, and language skills[1].

Pathological progression

Because APP, PSEN1, PSEN2, and MAPT mutations are present in a very small number of cases with early-onset AD (EOAD), the dual amyloidogenic-tauopathic theory of AD has dominated the pathogenic universe of AD-related neurodegeneration (and divided the research community as well) for the past 50 years.

However, this theory does not fully explain AD pathogenesis, and as a result, novel (or complementary) theories have been emerging during the past decades and in recent times[2,3].

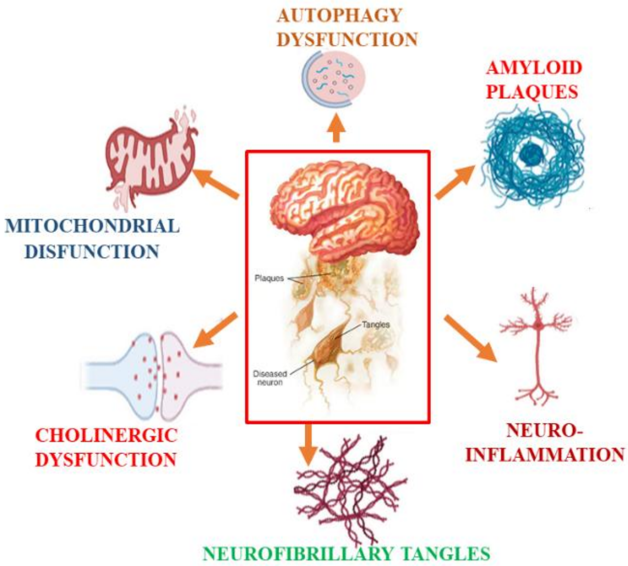

Figure 1: Elements that contribute to the development of Alzheimer's disease.

Genomic Defects

The "golden rule" of complex disorders, which states that the more genetic defects distributed in the human genome, the earlier the disease onset and the worse the response to conventional treatments; and the fewer pathogenic SNPs, the later the disease onset and the better the response to various pharmacological interventions, is fulfilled by AD, a complex polygenic/multifactorial disorder in which hundreds of polymorphic variants of risk may be involved.

Through the creation, destruction, or modification of microRNA (miRNA) binding sites, genetic variation linked to various disorders impedes the regulation of microRNA-mediated processes. In the adult human brain, miRNA-target variability is a common occurrence that may affect gene expression under both normal and pathological circumstances. AD-related SNPs alter susceptibility to AD by interfering with the control of miRNA genes. Target SNPs found in seven genes linked to the prognosis for AD are among the significant interactions with the miRNAs miR-214, -23a & -23b, -486-3p, -30e, -143, -128, -27a & -27b, -324-5p, and -422a. One factor contributing to the aberrant gene expression in AD is the dysregulated miRNA network.

Epigenetic Phenomena

The pathophysiology of complex illnesses, gene-gene and gene-environment interactions, and development and aging has all been shown to be significantly mediated by epigenetic factors. AD pathogenesis may be influenced by major epigenetic pathways, including noncoding RNA regulation, histone modifications and chromatin remodeling, and DNA methylation.

Cerebrovascular Dysfunction

Vascular and metabolic dysfunctions play a crucial role in Alzheimer's disease (AD) pathology, appearing early in the disease's progression. Cerebrovascular disease is more commonly observed in AD than in other neurodegenerative disorders, lowering the threshold for dementia. Early-stage indicators, such as global brain hypoperfusion, oxygen hypometabolism, and neurovascular decoupling, suggest early cerebral hemodynamic changes. Contributing factors include oxidative stress, amyloid-beta (Aβ) accumulation, genetic factors like the Ninjurin2 gene, and cardiovascular risks. Endothelial dysfunction and blood-brain barrier (BBB) breakdown lead to neuroinflammation, oxidative stress, and mitochondrial dysfunction, further exacerbating AD pathology. Chronic brain hypoperfusion can induce premature neuronal death. APOE-4 carriers show deficient brain hemodynamics compared to other variants.

Cerebral amyloid angiopathy (CAA) causes intra-cerebral hemorrhages and contributes to AD progression through amyloid plaque deposition in blood vessels. Reduced clearance of Aβ due to decreased P-glycoprotein expression and other transporters worsens Aβ accumulation. Additionally, AD patients, especially those using atypical antipsychotic drugs, show increased risk of transitory ischemic attacks (TIA), while vascular dementia (VD) patients have a higher risk of ischemic stroke.

Phenotypic Expression of Amyloid Deposits and Neurofibrillary Tangles (NFTs)

The external and intracellular expressions of the AD neuropathological phenotype are β-Amyloid deposits in senile and neuritic plaques and hyperphosphorylated tau proteins in NFTs, respectively. Additionally, there is selective neuronal loss in neocortical and hippocampal regions. The main (postmortem) diagnostic criterion for AD is the presence of an Aβ plaque in the brain. Aβ, a 39–43 amino acid peptide produced by the proteolytic cleavage of APP by β- and γ-secretases, is the primary constituent of senile plaques. Aβ is neurotoxic, and its aggregation state contributes to its neurotoxicity.

Neuronal Apoptosis

A pathognomonic finding in AD is neuronal loss, which is the last common pathway among several pathogenic processes leading to neurodegeneration in dementia. As far as structural brain biomarkers go, atrophy of the medial temporal lobe-particularly of the hippocampus and Para hippocampal gyrus is thought to be the most predictive. In contrast to the other parietal lobe regions, the medial and posterior regions appear to be more affected.

Neurotransmitter Deficits

A variety of neurotransmitter imbalances, including those caused by glutamate, acetylcholine, noradrenaline, dopamine, serotonin, and certain neuropeptides, have been suggested as the neurobiological cause of AD behavioral symptoms. The neurotransmission imbalance in AD is caused by altered neurotransmitter reuptake by vesicular glutamate transporters (VGLUTs), excitatory amino acid transporters (EAATs), the vesicular acetylcholine transporter (VAChT), the serotonin reuptake transporter (SERT), or the dopamine reuptake transporter (DAT). AD is associated with decreased levels of VGLUTs, EAAT1-3, VAChT, and SERT protein and mRNA[4].

Oxidative Stress

Oxidative damage is a key pathogenic mechanism in neurodegeneration, particularly in Alzheimer's disease (AD), where it is more pronounced than in age-matched controls. Antioxidant capacity increases with disease severity, correlating with the Braak tangle stage and the amount of insoluble amyloid-beta (Aβ). Aβ accumulation in the mitochondria of AD patients and transgenic mouse models leads to free radical generation and neuronal stress. The mitochondrial enzyme presequence protease (PreP), which degrades Aβ, shows reduced activity in AD brains and transgenic mouse models, potentially due to increased reactive oxygen species (ROS) production. This reduction in PreP activity may contribute to Aβ accumulation, mitochondrial toxicity, and neuronal death. In APP/PS1 mice, age-dependent increases in oxidative stress markers, loss of lipid asymmetry, and Aβ production are observed. Proteomic analysis of specific mouse models reveals age-dependent brain protein carbonylation targets, further highlighting the role of oxidative stress in AD pathology.

Cholesterol and Lipid Metabolism Dysfunction

Cholesterol is closely linked to the formation of amyloid plaques, a key feature in Alzheimer's disease (AD) pathology. Variants of the APOE gene, which influence cholesterol metabolism, play a significant role in the risk and progression of AD. Cholesterol has a protective effect against amyloid-beta (Aβ)-induced neuronal membrane disruption and inhibits β-sheet formation of Aβ on lipid bilayers. Genome-wide association studies have identified a significant association between pathways related to cholesterol metabolism and immune response in late-onset Alzheimer's disease (LOAD). Disturbances in intracellular lipid metabolism are observed in both cardiovascular and neurodegenerative diseases, influenced by genetic and lifestyle factors. Neural membranes contain various glycerophospholipids (GPs), which are crucial for membrane structure, fluidity, and ion permeability. GP degradation by phospholipase A2 releases important polyunsaturated fatty acids (PUFAs) like arachidonic acid and docosahexaenoic acid.

The oxidation of these PUFAs, both enzymatically and nonenzymatically, produces lipid mediators associated with neuronal pathways involved in AD neurobiology.

Neuroinflammation and Immunopathology

Genes related to immune regulation and inflammation, along with abnormal cytokine levels, are linked to Alzheimer's disease (AD). Inflammatory processes are a key aspect of AD pathology. Microglia, immune cells in the brain, is involved in the response to amyloid-beta (Aβ) deposits, but often fails to clear them effectively. Oligomeric Aβ is more toxic than its fibrillar form, although fibrillar Aβ can increase microglial activity. The TNF-α signaling pathway is crucial in AD-related inflammation, with altered levels of TNF-α observed in patients. The miR-181 family, especially in astrocytes, influences the inflammatory response; its overexpression can lead to increased cell death and altered cytokine production. The progression from mild cognitive impairment (MCI) to AD is associated with increased inflammatory activity, particularly involving the TNF-α signaling system[5].

Neurotoxic Factors

Various toxic agents, including metals like aluminum, copper, zinc, and iron, as well as biotoxins and pesticides, are believed to contribute to neurodegeneration. Dysregulated homeostasis of transition metals is implicated in Alzheimer's disease (AD) pathogenesis. The genotoxic metabolite methylazoxymethanol (MAM), derived from the cycad azoxyglucoside cycasin, causes genetic alterations across various organisms, though adult nerve cells were previously thought to be unaffected. However, research demonstrated that a single dose of MAM acetate in adult C57BL6 wild-type mice leads to DNA damage, specifically O6-methyldeoxyguanosine (O6-mG) lesions. This damage was exacerbated in mice lacking the DNA repair enzyme MGMT, resulting in increased O6-mG DNA damage. The DNA damage was associated with altered expression of genes involved in cell-signaling pathways linked to cancer, neurodegenerative diseases, and neurodevelopmental disorders[6].

Conclusion

The pathological progression of Alzheimer's disease involves the gradual accumulation of amyloid-beta plaques and tau tangles in the brain, leading to neuronal loss, synaptic dysfunction, and cognitive decline. This process typically results in memory impairment, personality changes, and loss of daily functioning, ultimately culminating in severe dementia. Supportive therapy, lifestyle modifications, and medication can all be used to manage Alzheimer's disease. Drugs like NMDA receptor antagonists (like memantine) and cholinesterase inhibitors (like donepezil, rivastigmine) can help reduce symptoms and decrease the condition's progression. A balanced diet, frequent exercise, and cognitive activities are examples of lifestyle modifications that may promote brain health. Non-drug methods of treating behavioral and psychological disorders include establishing regular routines and a peaceful atmosphere. Comprehensive care also includes education about the condition and support for caregivers. These techniques can enhance quality of life even when there is no cure.

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Article: 3

Pharmacogenomics in Alzheimer's Disease-related Dementia Treatment

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Abstract
The development of pharmacogenomics as an interdisciplinary large-scale systematic approach has been reinforced by the introduction of genomic techniques, such as genotyping, gene sequencing, gene expression, genetic epidemiology, transcriptomics, proteomics, metabolomics and bioinformatics, and other multiplex assay technologies, which allow deeper assessment of disease mechanisms, potential drug targets and metabolism, or associated pathway components. The incorporation of pharmacogenomic protocols to Alzheimer's disease (AD) research and clinical practice can foster therapeutics optimization by helping to develop cost-effective pharmaceuticals and improving drug efficacy and safety.
Keywords: Alzheimer disease, Pharmacogenomic, Genetic Research

Introduction
Pharmacogenomics, which studies how genetic variations affect drug responses, is revolutionizing Alzheimer's disease (AD) treatment by offering personalized and effective strategies. Genetic factors like the APOE ε4 allele and mutations in APP, PSEN1, and PSEN2 significantly impact disease progression and treatment response. Innovative approaches in drug development include designing targeted therapies, employing genetic biomarkers for drug discovery, and utilizing gene editing technologies. These advancements aim to address the complex and varied nature of AD, improve treatment outcomes, and manage the increasing economic and social burden of dementia, which poses significant challenges globally. The Human Genome Project and HapMap project have significantly advanced our understanding of human genetics, revealing the potential for identifying new biomarkers and improving predictive medicine. Pharmacogenomics, leveraging this genetic knowledge, aims to enhance drug efficacy and safety through DNA-based tests. Single nucleotide polymorphisms (SNPs) and their interactions across multiple genes offer insights into individual variability in drug responses, emphasizing the need for comprehensive genotyping. This evolving field combines genomics, pharmacology, and bioinformatics to address therapeutic failures and adverse drug effects by resolving disease mechanisms and guiding drug discovery. Although pharmacogenomics is making strides in treating neurodegenerative diseases like Alzheimer's, understanding the complex genetic and molecular mechanisms remains challenging. Research focuses on identifying key genes and their roles in drug responses, paving the way for targeted therapies and improved management of neurodegenerative disorders[1].

Genetics of Alzheimer’s disease
Genetic research has significantly advanced our understanding of Alzheimer’s disease (AD). Early-onset familial AD is caused by rare mutations in the APP and presenilin genes, leading to abnormal amyloid beta metabolism. In contrast, sporadic AD, more common and linked with aging, involves a range of susceptibility genes like APOE, A2M, IL1A, and TNF, among others. The APOE-4 allele is particularly associated with late-onset AD, influencing pathology through multiple mechanisms, including increased amyloid accumulation and tau phosphorylation. Other factors include polymorphisms in nicotinic receptors, oxidative stress genes, and inflammation-related genes. Genetic variations in neurotransmitter systems and neurodevelopmental genes, such as BDNF, also contribute to AD risk. These factors interact in complex genetic networks, leading to neurodegenerative processes like abnormal protein accumulation, oxidative stress, and synaptic dysfunction, ultimately resulting in neuronal death[2].

Pharmacogenomics's role in Alzheimer's disease-related dementia
The importance of genetics in Alzheimer's disease (AD) is growing, particularly in understanding how genetic variations affect drug response.

While AD treatment remains challenging, with current drugs only partially effective and often leading to side effects, pharmacogenomics offers a potential breakthrough. By tailoring treatments to individual genetic profiles, pharmacogenomics could improve drug efficacy and safety. Current AD treatments, including cholinesterase inhibitors and NMDA receptor antagonists, often show modest benefits and may interact adversely with other drugs due to genetic variations in drug-metabolizing enzymes, like CYP2D6.

Genetic profiling can help identify those most likely to benefit from specific drugs and avoid adverse effects. For example, the APOE-4 allele is linked to poorer responses to cholinesterase inhibitors, while other genotypes show better outcomes. Pharmacogenomics is advancing with the identification of new drug targets and the development of personalized treatment strategies. Genetic studies, including those using transgenic mouse models, are being utilized to explore new therapeutic approaches, such as anti-amyloid treatments and neuroprotective strategies.

As genetic knowledge expands, it becomes evident that AD treatment will need to account for genetic diversity among patients. Current research focuses on understanding how genetic variations influence drug response and developing therapies that can address the genetic underpinnings of the disease. The goal is to move towards more personalized, effective treatments by integrating genetic information into drug development and clinical practice[3].

Pharmacogenomics' applications and challenges

Pharmacogenomics holds significant promise for personalized medicine by tailoring drug treatments based on an individual's genetic profile. This approach enhances drug efficacy and minimizes adverse effects by ensuring that treatments are specifically suited to each patient's genetic makeup. By identifying genetic variants associated with drug responses, pharmacogenomics aids in the discovery of new drug targets and the development of medications that are more effective for particular genetic profiles. In drug development, pharmacogenomics contributes to optimizing drug dosage by understanding genetic differences in drug metabolism. This precision allows for more accurate dosing, reducing the risks of overdosing or under dosing. Additionally, it can help predict an individual's risk of developing certain conditions and their likely response to specific therapies, thus enabling proactive management and prevention strategies. Another important application is reducing adverse drug reactions. By identifying patients who are at higher risk of experiencing negative effects from certain drugs, pharmacogenomics helps avoid ineffective or harmful treatments, improving overall safety and efficacy in drug therapy.

Pharmacogenomics, while promising, faces several challenges. The intricate interactions of multiple genes and environmental factors complicate drug response predictions, requiring advanced analytical methods. Limited knowledge of genetic variants and their effects restricts broader application. Population diversity complicates generalizing findings, and integrating genetic data into clinical practice remains difficult. Ethical concerns about consent and discrimination, alongside high costs and accessibility issues, hinder widespread adoption. Additionally, regulatory and clinical hurdles, such as developing guidelines and training healthcare providers, need to be addressed to fully realize pharmacogenomics potential in personalized medicine[4].

Future perspective

Developing pharmacogenomics for CNS disorders involves identifying novel genetic factors and understanding gene networks to reveal disease mechanisms and therapeutic targets. Characterizing genetic polymorphisms across diverse populations is essential, as current studies focus primarily on SNPs and overlook polygenic effects. Establishing gene-gene and gene-environment models will enhance comprehension of complex disorders. Despite progress, pharmacogenomic studies lack replication in diverse populations and prospective trials, limiting their clinical application. Advances in functional genomics, proteomics, and bioinformatics are needed to drive progress in drug evaluation and personalized medicine. The implementation of pharmacogenomics in clinical practice can help optimize the limited therapeutic resources available to treat AD and personalize the use of anti-dementia drugs in combination with other medications for the treatment of concomitant disorders.

Conclusion

Pharmacogenomics holds promise for personalized Alzheimer's disease treatments by targeting genetic factors influencing drug responses. Advances in understanding gene interactions and developing high-throughput technologies are crucial. Overcoming current challenges will enable effective, individualized therapies, potentially transforming dementia care.

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Article: 4

Biomarkers for Alzheimer's disease

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Abstract

The search for meaningful biomarkers is one of the hottest areas of Alzheimer research. These biomarkers should be specific, suitable for routine use in clinical practice, and indicate specific stages of the disease. The emergence of novel biomarkers, such specific microRNA populations, downstream molecules associated with Amyloid-β (Aβ) and tau toxicity, and ultrasensitive detection of seeding-competent Aβ and tau populations are currently being explored for use as early, low-invasive, sensitive, and specific diagnostic probes. Currently under development, seeding aggregation assays are extremely sensitive techniques that exploit the functional properties of Aβ oligomers to seed the polymerization of monomeric Aβ. Recent advances in such innovative techniques may result in a blood-based diagnostic test for Alzheimer disease. Forthcoming research will reveal whether the coveted diagnostic test for Alzheimer disease is a real possibility.

Keywords: Alzheimer Research, Biomarkers, Amyloid-β

Introduction

Alzheimer's disease (AD) is a leading cause of dementia, beginning with mild memory issues that progress to severe cognitive impairment and functional decline. By the time AD is clinically diagnosed, significant neuronal loss and neuropathological changes are evident. Early intervention with neuroprotective drugs can potentially halt further damage, making early diagnosis crucial.

Identifying individuals with mild symptoms before full-blown dementia is essential. Current diagnostic approaches include imaging techniques and cerebrospinal fluid (CSF) biomarkers to classify AD. Given the projected increase in AD cases and associated costs from 2030 to 2050, research is focusing on early detection of the transition from normal aging and mild cognitive impairment (MCI) to dementia.

The concept of MCI has evolved, recognizing subtypes such as amnesic and non-amnesic, the latter involving executive function deficits like attention and problem-solving. Early AD diagnosis often involves analyzing the medial temporal lobe memory system, with memory impairments correlating with medial temporal lobe atrophy and hypoactivation[1].

Novel approaches such as mitochondrial electrophysiology and electrodermal activity analysis have the potential to identify early alterations in brain function prior to the manifestation of neuropathology or severe symptoms. Prodromal AD, Typical AD, Atypical AD, Mixed AD, and Preclinical States of AD are among the diagnostic classification categories that the National Institute on Aging and Alzheimer's Association has proposed. While typical AD is characterized by progressive memory deficits and cognitive problems, prodromal AD is characterized by early signs including episodic memory loss. Less prevalent phenotypes are associated with atypical AD, while concomitant illnesses are present in mixed AD. Alzheimer's pathology reflects early brain alterations, and presymptomatic AD and asymptomatic at-risk are the two categories of preclinical states[2].

Biomarkers and Risk Factors in Alzheimer's Disease

Visuospatial deficits and significant parietooccipital atrophy on MRI can indicate neurodegeneration leading to conditions such as posterior cortical atrophy or optical dysfunction in Alzheimer's Disease (AD). Symptoms commonly include logopenia, aphasia, and various forms of cognitive impairment. Additionally, presenile dementia and hemiparkinsonism can share features with AD, though their coexistence is rare.

Biomarkers are crucial for diagnosing AD, particularly when Mild Cognitive Impairment (MCI) is present. The accuracy of predicting AD in MCI patients improves when both Amyloid-β (Aβ) and neuronal injury biomarkers are positive. While Aβ alone provides an intermediate probability, the absence of Aβ measurement with a single neurologic damage biomarker suggests a lower likelihood of developing AD.

Age plays a significant role in AD progression, with pathological lesions density increasing with age. Early-onset familial AD, occurring before age 60, is inherited in an autosomal dominant manner and is linked to mutations in the amyloid precursor protein (APP) gene on chromosome 21. These mutations lead to Aβ plaque formation and are detectable in cerebrospinal fluid (CSF) and plasma using imaging techniques like Positron Emission Tomography (PET).

Key biomarkers include Aβ and phosphorylated tau proteins, which increase the likelihood of AD development. These biomarkers can be detected through various in vivo and in vitro methods, including Scanning Tunneling Microscopy and Optical Imaging. MRI and PET also reveal patterns of atrophy and hypometabolism in brain regions affected by AD.

Genetic factors, such as the presence of the Apolipoprotein E (ApoE) gene, especially its fourth form, increase AD risk, with age between 65 and 75 being particularly susceptible. Other biomarkers of interest include CSF α-synuclein and mitochondrial dysfunction, which affects ATP production and neuronal health. Metal ions, such as zinc, copper, and iron, contribute to oxidative stress and Aβ toxicity, influencing AD development[3].

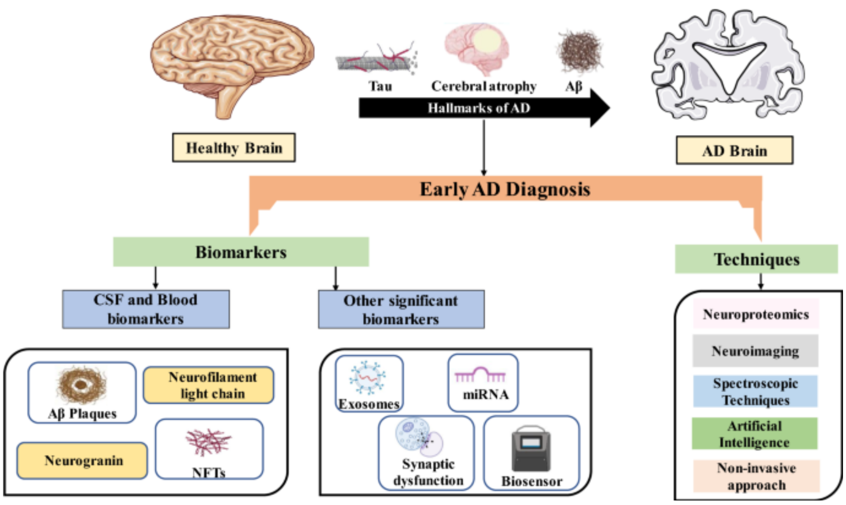

Figure 1: An overview of biomarkers and techniques for early diagnosis of Alzheimer's disease[4]

Recent studies also focus on novel biomarkers like YKL-40, elevated D-serine levels, and specific microRNAs (miR-31, miR-93, miR-143, and miR-146a) found in AD patients. Blood pressure changes are observed years before AD onset, though its exact role in disease progression remains unclear[3].

Overall, early and accurate diagnosis using a combination of biomarkers and imaging techniques is essential for managing AD and preventing its severe consequences.

Conclusion

Definitive diagnosis of Alzheimer's Disease (AD) requires post-mortem examination, as neuroimaging faces challenges due to clinical and pathological variability. While all AD patients experience a Mild Cognitive Impairment (MCI) phase, not all MCI patients develop AD, and progression rates vary. Biomarkers in cerebrospinal fluid and plasma, along with amyloid imaging, offer insights into AD neuropathology when structural MRI falls short. Genetic mutations contribute to less than 2% of cases, with age being a major risk factor. Early diagnosis using a combination of biomarkers and imaging is crucial for effective management and intervention.

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Article: 5

What Happens to the Brain in Alzheimer's Disease?

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Abstract

Alzheimer's disrupts processes vital to neurons and their networks, including communication, metabolism, and repair. It's characterized by changes in the brain that lead to deposits of certain proteins. At first, Alzheimer's usually damages the connections among neurons in parts of the brain involved in memory, including the entorhinal cortex and hippocampus. Damage to nerve cells in the brain can also make it difficult for the person to express thoughts and perform routine tasks without assistance. Alzheimer's disease causes the brain to shrink and brain cells to eventually die. The person in the final months of Alzheimer's disease will experience increased mental and physical deterioration, eventually needing 24-hour care.

Keywords: Alzheimer, Alzheimer's Disease, Entorhinal cortex, Hippocampus

Introduction

Alzheimer's disease primarily affects the brain by causing progressive degeneration of nerve cells, leading to cognitive decline, memory loss, and changes in behavior. Brain is our most powerful organ, yet weighs only about three pounds. It has a texture similar to firm jelly.

In the brain the cerebrum fills up most of your skull. It is involved in remembering, problem solving, thinking, and feeling. It also controls movement. The cerebellum sits at the back of your head, under the cerebrum. It controls coordination and balance. The brain stem sits beneath your cerebrum in front of your cerebellum.
Alzheimer's disease profoundly affects the brain, leading to significant cognitive decline and behavioral changes. The disease primarily targets neurons, disrupting their function and eventually causing cell death. The main things of Alzheimer's disease include the accumulation of amyloid plaques and tau tangles, which interfere with neural communication and contribute to neuronal damage. As the disease progresses, it impacts various brain regions, beginning with the hippocampus, which is essential for memory formation. This leads to early symptoms like memory loss and confusion. Over time, the disease spreads to other areas of the brain, affecting functions such as language, reasoning, and spatial abilities[1].

Etiology

Amyloidal Plaques

Formation of Plaques: Alzheimer’s disease is characterized by the accumulation of amyloid-beta protein plaques between nerve cells (neurons) in the brain. These plaques disrupt cell-to-cell communication.

Neuronal Damage: The buildup of plaques can trigger an inflammatory response and lead to neuronal damage and death.

Neurofibrillary Tangles

Tau Protein Tangles: Another hallmark of Alzheimer’s is the formation of neurofibrillary tangles inside neurons. These tangles are composed of abnormally phosphorylated tau proteins.

Disruption of Nutrient Transport: The tangles disrupt the transport system within neurons, which is essential for moving nutrients and other important substances within the cell. This disruption contributes to cell death.

Loss of Synapses

Synaptic Loss: Alzheimer’s leads to the loss of synapses, the connections between neurons. This loss impairs communication between neurons, affecting learning and memory.

Reduction in Neurotransmitters: There is a significant reduction in neurotransmitters, such as acetylcholine, which are crucial for memory and learning processes.

Brain Atrophy

Shrinkage of Brain Tissue: As neurons die, the brain tissue shrinks, leading to atrophy. This shrinkage is particularly noticeable in the hippocampus, which is responsible for forming new memories.

Enlarged Ventricles: The loss of brain tissue results in the enlargement of the brain's ventricles (fluid-filled spaces) [2,3].

Symptoms

Memory Loss: Short-term memory is typically affected first, with patients having difficulty recalling recent events. Over time, long-term memory is also impacted.

Cognitive Decline: Patients experience declines in various cognitive functions, including reasoning, problem-solving, and judgment.

Language Impairment: There is a gradual deterioration in language abilities, including difficulty finding the right words, forming coherent sentences, and understanding spoken and written language.

Mood Changes: Patients may experience mood swings, depression, and anxiety.

Behavioral Changes: Changes in behavior, such as increased agitation, aggression, and wandering, are common as the disease progresses.

Hallucinations and Delusions: In advanced stages, patients may experience hallucinations and delusions[2,3].

Stages of Progression

Preclinical Stage: Changes in the brain begin years before symptoms appear. This stage is characterized by the accumulation of amyloid plaques and tau tangles without noticeable symptoms.

Mild Cognitive Impairment (MCI): Patients have mild but noticeable changes in memory and cognitive abilities. These changes are not severe enough to interfere significantly with daily life[2,3].

Conclusion

The cumulative effect of these pathological changes results in the hallmark symptoms of Alzheimer's, including severe memory impairment, disorientation, and changes in behavior and personality. Ultimately, Alzheimer's disease leads to a decline in the ability to perform daily activities and requires comprehensive care and support. Research continues to seek better understanding, early detection, and effective treatments for Alzheimer's disease. Advances in these areas hold the promise of mitigating the impact of the disease and improving the quality of life for those affected and their caregiver.

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Article: 6

Blood Test Shows Promise for Alzheimer’s Diagnosis

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Abstract

Alzheimer's disease is the most common type of dementia. It is a progressive disease beginning with mild memory loss and possibly leading to loss of the ability to carry on a conversation and respond to the environment. A simple blood test shows promise as a way to detect Alzheimer’s disease, which could drastically improve the accuracy and speed of diagnoses. Currently, Alzheimer’s is diagnosed via a mixture of memory and cognitive tests, as well as brain imaging and lab tests. While some blood tests have shown promise as a diagnostic tool, they are hindered by their complexity. A simple blood test has been shown to detect Alzheimer’s disease in routine health care settings with up to 90% accuracy, according to Swedish researchers. The findings were presented at the Alzheimer’s Association International Conference in Philadelphia. The findings could speed the quest for an affordable and accessible way to diagnose patients with memory problems.

Keywords: Alzheimer's disease, Alzheimer’s diagnosis, Blood test

Introduction

Alzheimer’s disease[1] is a brain disorder that slowly destroys memory and thinking skills, and eventually, the ability to carry out the simplest tasks. In most people with Alzheimer’s, symptoms first appear later in life. There is currently no cure, but there are ways to support a person through medication and other strategies. Approximately one in five women and one in 10 men develop dementia due to Alzheimer’s disease, according to the Alzheimer’s Association[2].

Common symptoms of Alzheimer’s disease include memory loss, language problems, and impulsive or unpredictable behaviour. One of the main features of the condition is the presence of plaques and tangles in the brain. Another feature is a loss of connection between the nerve cells, or neurons, in the brain. These features mean that information cannot pass easily between different areas of the brain or between the brain and the muscles or organs. As the symptoms worsen, it becomes harder for people to remember recent events, to reason, and to recognize people they know[3].

Eventually, a person with Alzheimer's disease may need full-time assistance. Alzheimer's disease is the most common type of dementia. It involves plaques and tangles forming in the brain. Symptoms start gradually and are most likely to include a decline in cognitive function and language ability. No disease-modifying drugs are available for Alzheimer's disease, but some options may reduce the symptoms and help improve quality of life. Drugs called cholinesterase inhibitors can ease cognitive symptoms, including memory loss, confusion, altered thought processes, and judgment problems. They improve neural communication across the brain and slow the progress of these symptoms.

Methodology

In a study published in the Journal of the American Medical Association[4], the researchers said their new method accurately detected signs of Alzheimer's in around 90% of patients. Researchers reported that a blood test was significantly more accurate than doctors' interpretation of cognitive tests and CT scans in signaling the condition. Dementia specialists using standard methods that did not include expensive PET scans or invasive spinal taps were accurate 73 percent of the time, while primary care doctors using those methods got it right only 61 percent of the time. The blood test's accuracy was highest with patients who had already progressed to dementia and was slightly lower with patients in a pre-dementia stage called mild cognitive impairment

Results

Blood test based on the ratio of plasma phosphorylated tau 217 (p-tau217) relative to non–p-tau217 (expressed as percentage of p-tau217) combined with the amyloid-β 42 and amyloid-β 40 plasma ratio (the amyloid probability score 2 [APS2]) accurately identify Alzheimer disease in primary care and secondary care.

There were 1213 patients undergoing cognitive evaluation in primary or secondary care. The APS2 had high diagnostic accuracy (range, 88%-92%) for detecting Alzheimer disease pathology in both primary and secondary care. Dementia specialists identified clinical Alzheimer disease with a diagnostic accuracy of 73% vs 91% using the APS2 and primary care physicians had a diagnostic accuracy of 61% vs 91% using the APS2.

The patients then underwent both the blood test and cerebrospinal fluid tests, and researchers compared the results. The test works by measuring the levels of Plasma Phospho-Tau217, a biomarker that is linked to the presence of Alzheimer's pathology in the brain. By comparison, the blood test had an accuracy of 90%. The main limitation of the research was that it was only conducted in Sweden. It has been shown to detect the disease even before the person begins experiencing symptoms.

The biomarker, known as plasma phosphorylated tau 217 (or p-tau217), can also be found in cerebrospinal fluid, but extracting that is a more difficult process than blood. The test also looked at the ratio of two components of a plaque that forms in the brains of people with Alzheimer's. If the p-tau217 was found in a sample along with a certain ratio of the plaque components, the researchers theorized it would lead to conclusive evidence that a patient had the disease[5].

The APS2 and percentage of p-tau217 alone had high diagnostic accuracy for identifying AD among individuals with cognitive symptoms in primary and secondary care using predefined cutoff values. Future studies should evaluate how the use of blood tests for these biomarkers influences clinical care.

Conclusion

The new study used a blood test that focuses on a form of a protein called tau that sprouts into tangles in the brains of people with Alzheimer's. Medical experts say the findings bring the field closer to a day when people might receive routine blood tests for cognitive impairment as part of primary care checkups, similar to the way they receive cholesterol tests. The findings could speed the quest for an affordable and accessible way to diagnose patients with memory problems.

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Article: 7

Sleep Disturbances by Alzheimer's Disease

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Abstract

Sleep disturbances, as well as sleep-wake rhythm disturbances, are typical symptoms of Alzheimer's disease (AD) that may precede the other clinical signs of this neurodegenerative disease. Typical disturbances of the neurophysiological sleep architecture in the course of the AD include deep sleep and paradoxical sleep deprivation. Factors that might contribute to sleep disturbances and sundowning include mental and physical exhaustion at the end of the day. Many people with Alzheimer's wake up more often and stay awake longer during the night. It is quite common for a person, especially in the later stages, to spend a lot of their time sleeping both during the day and night. This can sometimes be distressing for the person's family and friends, as they may worry that something is wrong.

Keywords: Alzheimer's disease, Sleep disturbances, Insomania

Introduction

Alzheimer's disease, it is a devastating neurodegenerative condition, that affects millions of people worldwide. While genetics and age are well-known risk factors, recent research has highlighted the significant role that sleeps plays in the development and progression of Alzheimer's disease. It is clear that the connection between sleep and Alzheimer's is crucial for developing preventive strategies and improving the quality of life for those at risk.

Among sleep disorders occurring in patients with AD, the most frequent disorders are sleep breathing disorders and restless legs syndrome. Sleep disorders may influence circadian fluctuations of the concentrations of amyloid-β in the interstitial brain fluid and in the cerebrovascular fluid related to the glymphatic brain system and production of the amyloid-β[1].

The Importance of Sleep for Brain Health

Sleep is essential for overall health and well-being, particularly for brain function. During sleep, the brain undergoes vital processes such as memory consolidation, waste clearance, and the regulation of various cognitive functions. Adequate and high-quality sleep is necessary for maintaining these processes and ensuring optimal brain health.

Sleep and Amyloid-Beta Clearance

One of the hallmark features of Alzheimer's disease is the accumulation of amyloid-beta plaques in the brain. These toxic protein aggregates disrupt neural communication and contribute to cognitive decline. Studies have shown that sleep plays a critical role in the clearance of amyloid-beta from the brain. During deep sleep, the brain's glymphatic system becomes more active, facilitating the removal of waste products, including amyloid-beta. Conversely, poor sleep or sleep disorders can impair this clearance mechanism, leading to the buildup of amyloid-beta and increasing the risk of Alzheimer's disease[1,3].

The Impact of Sleep Disorders on Alzheimer's Risk

Sleep Apnea

Sleep apnea, a condition characterized by repeated interruptions in breathing during sleep, is associated with an increased risk of Alzheimer's disease. The intermittent hypoxia (lack of oxygen) and sleep fragmentation caused by sleep apnea can lead to inflammation, oxidative stress, and neuronal damage, all of which contribute to cognitive decline. Effective treatment of sleep apnea, such as continuous positive airway pressure (CPAP) therapy, can improve sleep quality and potentially reduce Alzheimer's risk.

Insomnia

Insomnia, a common sleep disorder characterized by difficulty falling asleep or staying asleep, is also linked to an increased risk of Alzheimer's disease. Chronic insomnia can lead to prolonged periods of sleep deprivation, which negatively impacts cognitive function and accelerates the accumulation of amyloid-beta. Implementing good sleep hygiene practices, cognitive-behavioral therapy for insomnia (CBT-I), and, in some cases, medication can help manage insomnia and improve sleep quality.

Sleep Quality and Cognitive Function

Even in the absence of sleep disorders, poor sleep quality can adversely affect cognitive function. Fragmented sleep, frequent awakenings, and reduced time spent in deep sleep stages can impair memory, attention, and executive function. These cognitive impairments can increase the susceptibility to Alzheimer's disease. Prioritizing healthy sleep habits, such as maintaining a consistent sleep schedule, creating a restful sleep environment, and avoiding stimulants before bedtime, can support better sleep quality and cognitive health[2,3].

Strategies for Improving Sleep and Reducing Alzheimer's Risk

Establishing a Sleep Routine

Creating and maintaining a consistent sleep routine is crucial for promoting healthy sleep patterns. Going to bed and waking up at the same time each day helps regulate the body's internal clock and improve sleep quality. Establishing a calming pre-sleep routine, such as reading or taking a warm bath, can signal to the body that it is time to wind down and prepare for sleep.

Creating a Sleep-Conducive Environment

The sleep environment plays a significant role in sleep quality. Ensuring a cool, dark, and quiet bedroom can promote better sleep. Investing in a comfortable mattress and pillows, as well as minimizing electronic device use before bedtime, can also enhance sleep quality.

Managing Stress and Anxiety

Chronic stress and anxiety can disrupt sleep and negatively impact cognitive health. Incorporating stress management techniques, such as mindfulness meditation, deep breathing exercises, and regular physical activity, can help reduce stress levels and improve sleep quality. Seeking professional support, such as therapy or counseling, may also be beneficial for managing stress and anxiety[2,3].

Conclusion

The link between sleep and Alzheimer's disease underscores the importance of prioritizing good sleep habits for maintaining cognitive health. By understanding the mechanisms through which sleep affects brain function and implementing strategies to improve sleep quality, individuals can take proactive steps to reduce their risk of Alzheimer's disease. As research continues to uncover the intricate relationship between sleep and neuron degeneration, promoting healthy sleep practices will remain a key component of Alzheimer's prevention and overall brain health.

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About RKDF University Ranchi

It was in the year 2018, **Dr. Sunil Kapoor**, the founder decided to fulfil his dream of establishing an institute for quality education to the people and the region & beyond initiated **"Ayushmati Education and Social Society"** trust in an attempt to make the holy city of Ranchi, a recognized destination for knowledge seekers from different spheres of life and strive to become one of the best Universities in Jharkhand. This is what led to the foundation of a milestone at the karmabhoomi of the versatile and sagacious **Bhagwan Birsa Munda**.

RKDF group has been actively involved with social causes since its very inception and has drawn appreciation from one and all for its works in various facets of societal paradigms. The Group started its journey in 1994 by establishing 1st private engineering college at Bhopal, Madhya Pradesh. Now the group has 162 institutions & 6 universities (Five in Madhya Pradesh and one in Jharkhand). The six universities and social society established by Ayushmati Education are **RKDF University, Bhopal** (2011), **Sri Satya Sai University of Technology & Medical Science, Sehore** (2014), **Sarvepalli Radhakrishna University, Bhopal** (2015), **Dr. A.P.J. Abdul Kalam University, Indore** (2016), **Bhabha University, Bhopal** (2018), **RKDF University, Ranchi** (2018). RKDF Ranchi is a highly prestigious government recoginized university established under the Jharkhand Govt. Act & registered under UGC 2f 1956. RKDF University, Ranchi is a recoginized member of AIU (Association of Indian Universities) and has publication house, named IJHESM (International Journal of Humanities, Engineering, and Science & Management) with an impact factor of SJIF-5.81.

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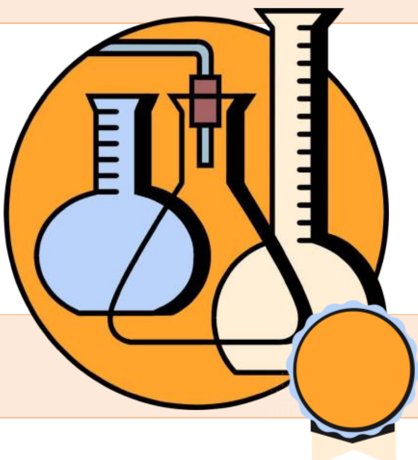
Deadline for article submissions: 30th Sept. 2024 Send your article on (only micro soft doc file) pharmacy@rkdfuniversity.org	
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