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Review Article

Review on Alzheimer's disease

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ABSTRACT

The treatment of behavioral and psychological symptoms of dementia (BPSD) in Alzheimer's disease (AD) is crucial for individuals with the condition. Cholinesterase inhibitors (CIs) and memantine, used for cognitive symptoms, may have some effect on BPSD, but additional drugs may be needed as BPSD worsens. Selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, sertraline, and others are effective antidepressants for comorbid depression in AD. Limited evidence supports their use for treating depression, agitation, and psychosis in AD, but recent trials showed no benefit and increased risks. Non-pharmacological interventions such as psycho social approaches and alternative therapies are important. A comprehensive approach combining medication and non-pharmacological interventions, along with close monitoring, is essential for managing BPSD and improving quality of life for individuals with AD and their caregivers.

1. Introduction

Alzheimer's disease (AD) is indeed the most common type of dementia, characterized by a gradual and progressive decline in cognitive function. It is named after the German psychiatrist Alois Alzheimer, who first described the disease in the early 20th century.[1] Alzheimer observed certain pathological features, including the presence of neuritic plaques and neurofibrillary tangles, in the brain of his patient who exhibited symptoms of memory loss and personality changes. These pathological features are primarily associated with the accumulation of a protein called amyloid-beta peptide (Aβ) in the brain, particularly in the medial temporal lobe and neocortical structures.[2]

The amyloid plaques are composed of aggregated Aβ protein, while neurofibrillary tangles consist of twisted tau protein fibers inside brain cells.[3,4] These abnormal protein deposits disrupt normal cellular processes and communication between neurons, leading to cognitive impairment and the eventual loss of brain tissue. The exact cause of Alzheimer's disease is still not fully understood, but it is believed to involve a combination of genetic, environmental, and lifestyle factors.[5]

While Alzheimer's disease is a significant contributor to progressive cognitive decline, it is important to note that other factors can also lead to the loss of cognitive functions. Intoxications, infections, pulmonary and circulatory abnormalities reducing oxygen supply to the brain, nutritional deficiencies, vitamin B12 deficiency, tumors, and various other conditions can cause cognitive impairment.[6–8] It is crucial for healthcare professionals to evaluate and consider all potential causes when diagnosing cognitive decline in individuals.

Early diagnosis and appropriate management are important in Alzheimer's disease and other conditions causing cognitive decline. Medical professionals can conduct a thorough evaluation, including medical history, physical examination, and cognitive tests, to determine the

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underlying cause and develop an appropriate treatment plan or interventions.[9,10]

2. Diagnosis

Alzheimer's disease (AD) typically progresses slowly, with an average decline of 3 to 4 points per year on cognitive assessment tests like the Mini-Mental State Examination (MMSE). The disease often begins with subtle memory loss and later manifests as difficulties in language (aphasia), motor skills (apraxia), and recognizing familiar objects (agnosia) after several years. Early stages may also involve irritability and personality changes.[11] As the disease advances, patients may experience gait and motor disturbances and eventually become mute and bedridden. On average, individuals with AD live for 8 to 10 years after diagnosis, but the disease can last up to 20 years.[8]

The preclinical stage of AD refers to the phase where individuals do not yet show clinical symptoms but have biological markers indicating the disease process. Biomarkers such as amyloid buildup and changes in nerve cells can be detected in some individuals through imaging, glucose utilization changes, or cerebrospinal fluid levels of certain proteins. At this stage, intervention may have a higher chance of modifying the disease. However, the risk of progression to Alzheimer's dementia is currently unknown for individuals in the preclinical stage.[12]The use of biomarker tests in this stage is primarily recommended for research purposes, as the data and standardization of these tests are still being developed.

When investigating potential Alzheimer's disease (AD) in a patient, several tests are conducted. These include a neurological examination, magnetic resonance imaging (MRI) to evaluate brain structure, and laboratory tests such as measuring vitamin B12 levels.[13] Studies have shown that vitamin B12 deficiency is associated with neurological problems and an increased risk of AD. High levels of homocysteine, a marker of B12 deficiency, can lead to brain damage through oxidative stress, increased calcium influx, and apoptosis. To diagnose B12 deficiency, serum B12 levels, complete blood count, and homocysteine levels are measured.

In 1984, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) collaborated to establish clinical diagnostic criteria for AD.[14]These criteria identify probable AD based on dementia confirmed by neuropsychological tests, progressive memory loss, impaired daily functioning, and other symptoms such as aphasia, apraxia, and agnosia. Possible AD can be diagnosed if there is no evidence of neurological or psychiatric disorders and another illness is not the primary cause of dementia. Definite AD is confirmed through histopathologic examination obtained from a biopsy or autopsy.

In 2011, the National Institute on Aging—Alzheimer's Association updated the NINCDS-ADRDA criteria to improve the accuracy of AD diagnosis. The updated criteria include probable and possible AD dementia for clinical settings, as well as probable or possible AD dementia with pathophysiological evidence for research purposes, utilizing clinical biomarkers. Biomarkers for AD can be categorized as brain amyloid markers (e.g., PET and CSF) and markers of neuronal injury (e.g., CSF tau, FDG-PET for metabolic activity, and MRI for measuring brain atrophy). These biomarkers play a crucial role in the diagnosis and research of AD.[15,16]

3. Stages of Alzheimer's Disease

The rationale for focusing on preclinical stage Alzheimer's disease (AD) is based on several factors. First, the pathobiological onset of AD is clinically silent, meaning that there are no noticeable symptoms in the early stages. It takes years before patients begin experiencing memory impairment that exceeds that of their age-peers, a stage called mild cognitive impairment (MCI), and several more years before their cognitive skills decline to a functionally disabling degree, marking the clinical onset of dementia.[17]

In terms of neuropathological features, fibrillar amyloid deposition, one of the defining characteristics of AD, is nearly maximal by the MCI stage, while neurofibrillary tangle formation continues to advance along with cerebral atrophy and progressive dementia severity.[18]Current therapeutic approaches targeting established cognitive deficits or patients with frank dementia may be too late or less relevant to disease initiation and early progression. Therefore, there is a need to focus on preclinical AD, intervening prior to or early in the amyloid cascade when patients are still asymptomatic.

Treating asymptomatic individuals who may develop AD in the future is conceptually and operationally challenging. It requires a better understanding of what distinguishes preclinical AD from normal aging and when symptoms are most likely to emerge. Age is a significant risk factor for AD, but genetic insights have improved our understanding of disease risk and could help design preclinical AD trials. Genetic factors, such as mutations in genes like amyloid-beta protein precursor (AβPP), presenilin-1 (PS1), and presenilin-2 (PS2), and the APOE $\varepsilon 4$ allele, play a role in AD susceptibility.[19]

Neuropathological studies have shown overlap between normal aging and AD, with neurofibrillary tangle formation considered part of normal aging, particularly in the entorhinal cortex. However, neocortical NFT formation is associated with AD or other tauopathies.[11,20]Amyloid deposition, on the other hand, begins in neocortical regions and can be found in both AD and non-demented individuals, suggesting that it may be part of normal or pathological aging. Additionally, brain imaging techniques, such as

structural magnetic resonance imaging (MRI) and positron emission tomography (PET), can detect early brain changes associated with AD, including reductions in regional brain tissue volume and glucose metabolism, and the presence of fibrillar amyloid burden.

Cerebrospinal fluid (CSF) biomarkers have also been studied in AD, showing characteristic abnormalities in later preclinical and clinical stages, such as reductions in CSF Aβ1-42 levels and elevated total-tau or phospho-tau levels. These biomarkers can provide insights into the trajectory of AD-related changes and help define the preclinical stages of the disease.

So, focusing on preclinical stage AD is crucial for optimizing disease modification strategies and developing effective therapies. Intervention at an early stage, before the onset of symptoms, may be necessary to slow the progression of AD. Genetic factors, neuropathology, brain imaging, and CSF biomarkers contribute to distinguishing preclinical AD from normal aging and identifying individuals at increased risk for symptomatic conversion.[21]

4. Causes and Risk Factors of Alzheimer's Disease

Alzheimer's disease is influenced by multiple risk factors, including age, genetics, head injuries, vascular diseases, infections, and environmental factors. The exact cause of the pathological changes in AD, such as the accumulation of Aβ plaques, NFTs, and synaptic loss, remains unknown.[22]

Two main hypotheses have been proposed to explain AD development. The cholinergic hypothesis suggests that a decline in cholinergic function, particularly the degeneration of cholinergic neurons, contributes to cognitive decline in AD.[23] The amyloid hypothesis suggests that imbalances in the production and clearance of amyloid-beta protein lead to the buildup of toxic Aβ plaques, initiating a cascade of events that result in neurodegeneration.

It's important to note that these hypotheses are not mutually exclusive, and there are likely other factors and mechanisms involved in AD pathogenesis. Given the complexity of the disease and the involvement of multiple risk factors, it is challenging to establish a single cause or develop a comprehensive theory of AD. Ongoing research continues to investigate the intricacies of the disease in order to identify effective therapeutic strategies.[24]

5. Alzheimer's Disease Hypotheses

5.1. Cholinergic hypothesis

1. Cholinergic deficits and the enzyme choline acetyltransferase (ChAT) are linked to Alzheimer's disease (AD).
2. Acetylcholine (ACh) plays a crucial role in cognitive function, and its deficiency leads to cognitive decline and memory loss.
3. β-amyloid (Aβ) affects cholinergic neurotransmission and leads to reduced choline uptake and ACh release.
4. Cholinergic synaptic loss and amyloid fibril formation are related to Aβ oligomers' neurotoxicity and interactions between AChE and Aβ peptide.
5. Other factors like reduced nicotinic and muscarinic Ach receptors and deficits in excitatory amino acid neurotransmission contribute to AD progression.[25–27]

5.2. Amyloid hypothesis

1. Abnormal deposition of β-sheets in the central nervous system is correlated with dementia, leading to the amyloid hypothesis.
2. Amyloid plaques (AP) also deposit in normal aging brains, questioning the role of AP deposition in AD onset.
3. The amyloid hypothesis suggests that the accumulation of Aβ peptides, particularly Aβ42, leads to neurotoxicity, tau pathology, and neuronal cell death.
4. Mutations in genes like APP, PSEN1, and PSEN2 affect Aβ catabolism and anabolism, leading to Aβ accumulation and neurodegeneration.[28,29]

6. Alzheimer's Disease Risk Factors

6.1. Aging

1. Aging is the most important risk factor for AD, with late-onset cases typically occurring after the age of 65.
2. Aging involves brain volume and weight reduction, synapse loss, ventricle enlargement, β-amyloid deposition, and neurofibrillary tangles (NFT).
3. Conditions like glucose hypometabolism, cholesterol dyshomeostasis, mitochondria dysfunction, depression, and cognitive decline may emerge during aging.[30]

6.2. Genetics

1. Genetic factors play a major role in AD, with approximately 70% of cases related to genetic factors.
2. Mutations in genes like APP, PSEN1, PSEN2, and ApoE are associated with AD.
3. APP mutations lead to Aβ accumulation, while the A673T mutation is protective.
4. PSEN1 and PSEN2 mutations affect γ-secretase activity, leading to increased Aβ42/Aβ40 ratio.
5. ApoEε4 allele is a strong risk factor for both early-onset and late-onset AD.
6. Other genes like ABCA1, CLU, BIN1, ECSIT, and ESR are also associated with AD risk.[31,32]

This highlights the risk factors associated with AD, including aging and genetic factors such as mutations in genes like APP, PSEN1, PSEN2, and ApoE. The summary

provides a concise understanding of these hypotheses and risk factors, which are crucial for further research and potential therapeutic interventions for Alzheimer's disease.

6.3. Treatment of behavioral and psychological symptoms of dementia in Alzheimer's disease

noncognitive neuropsychiatric symptoms, also known as behavioral and psychological symptoms of dementia (BPSD), in Alzheimer's disease (AD) and amnestic mild cognitive impairment (MCI). These symptoms are common throughout the clinical stages of AD and tend to increase in prevalence as the disease progresses. BPSD is a major contributor to caregiver burden and can lead to institutionalization of patients.[33]

Observational studies have identified four major symptom clusters with high prevalence in BPSD: psychosis (e.g., delusions), affective symptoms (anxiety and depression), hyperactivity (aggression, disinhibition), and apathy. While cholinesterase inhibitors (CIs) and memantine may have some effect on behavioral symptoms, their efficacy may decrease as BPSD becomes more severe. Additional drugs may be necessary to address these symptoms.

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, sertraline, paroxetine, citalopram, and fluvoxamine are considered effective antidepressants for comorbid depression in AD dementia. Other commonly used antidepressants in this population include mirtazapine, venlafaxine, duloxetine (combined selective noradrenaline and serotonin inhibitors or SNRIs), and bupropion. Limited clinical trials and meta-analyses support their efficacy in treating depression in AD dementia. SSRIs may also be considered for the treatment of agitation and psychosis in AD dementia. However, a recent trial (HTA-SADD) with sertraline or mirtazapine showed no benefit compared to placebo and increased risk of adverse events, leading to a reevaluation of the current practice of using these antidepressants as first-line treatment for depression in Alzheimer's disease.[34]

Antipsychotics are commonly used to treat psychotic symptoms and agitation/aggression in AD dementia. Atypical antipsychotics such as olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole are preferred due to their milder parkinsonian effects. However, the use of antipsychotics in dementia has been controversial due to findings of increased cerebrovascular morbidity, higher mortality, risk of hip fracture, pneumonia, and worsening cognitive impairment. Short-term use of antipsychotics may reduce mortality, and stopping the medication may not lead to a subsequent increase in BPSD.

Benzodiazepines are used to reduce agitation and anxiety but can also trigger further agitation in older individuals. Greater benzodiazepine use has been associated with more rapid cognitive and functional decline in AD and older adults in general.

Anticonvulsant drugs like carbamazepine can partially reduce BPSD in AD. However, the current drugs used for AD treatment have limited beneficial effects on cognitive function and provide only some relief for BPSD. There is a recognized medical need for the development of new drugs that act during the early stages of AD because early intervention is crucial to prevent irreversible symptom progression.

6.4. Disease-modifying approaches to Alzheimer's disease

Alzheimer's disease (AD) is characterized by the production of amyloid-beta (Aβ) and the formation of senile plaques (SPs) as well as the accumulation of abnormal tau protein leading to neurofibrillary tangles (NFTs). These processes are key components of AD pathogenesis. Targeting Aβ and tau has been the focus of disease-modifying approaches in AD. Potential strategies include reducing Aβ and tau production, preventing their aggregation or misfolding, neutralizing or removing toxic forms of these proteins, or using a combination of these approaches.[33–35]

In addition to Aβ and tau, other mechanisms have been implicated in AD pathology. These mechanisms include inflammation, oxidative damage, iron deregulation, and cholesterol metabolism. These processes may interact with Aβ plaques and NFT formation, further contributing to the progression of AD.

Understanding and targeting these various pathogenic mechanisms holds promise for the development of disease-modifying therapies for AD. By addressing multiple aspects of AD pathology, it may be possible to prevent or effectively treat the disease. Further research is needed to explore these therapeutic strategies and their potential for clinical application.[35]

Immunotherapy shows promise for treating Alzheimer's disease by targeting amyloid plaques, but the exact mechanisms are not fully understood. Active and passive immunization approaches are being studied, with some monoclonal antibodies showing potential benefits. New vaccines and antibodies are also being developed. Further research is needed to optimize treatment and ensure long-term safety and efficacy. Immunotherapy holds potential as a disease-modifying therapy for Alzheimer's by addressing the underlying pathology.[36]

6.5. Drugs interfering with tau deposition

Several compounds have been identified as inhibitors of tau aggregation, including methylene blue (MB). MB, currently being evaluated in Alzheimer's disease (AD) trials, has shown promising results in a phase II clinical trial, with reported improvements in cognitive function after 6 months of administration in AD patients. However, the drug can

cause urine discoloration, leading to a lack of blinding.[37]

6.6. Drugs interfering with tau phosphorylation

The hyperphosphorylation of tau protein is associated with tau pathology in Alzheimer's disease (AD), leading to the investigation of kinase inhibitors as potential therapeutics. Glycogen synthase kinase 3 (GSK3β) has been identified as a potential target, with lithium being the most studied compound inhibiting GSK3. Other compounds, such as pyrazolopyrazines, pyrazolopyridines, AR-A014418, and sodium valproate, are also under development. Short-term treatment with lithium has shown positive effects on cognitive and biological outcomes in individuals with amnestic mild cognitive impairment (MCI), suggesting its potential as a disease-modifying treatment for AD.[38]

7. Disease-modifying Treatments: Additional Approaches

7.1. Modulation of Cholesterol and Cascular-related Risk Factors

Modulating cholesterol and vascular-related risk factors is being explored as a potential disease-modifying approach for Alzheimer's disease (AD). Some studies suggest a link between hypercholesterolemia, cardiovascular diseases, and AD. Cholesterol-lowering therapy with statins has shown some promising results in reducing the prevalence of AD. However, clinical trials testing the effectiveness of statins in AD patients have not consistently shown significant benefits. Ongoing trials are investigating the use of simvastatin to slow the progression of AD, but results have not been published yet. A recent trial of simvastatin in individuals with mild to moderate AD and normal lipid levels did not show significant benefits on disease progression despite lowering cholesterol levels.[39]

8. Conclusions

Alzheimer's disease (AD) is a global health concern, and updated diagnostic criteria have been proposed for better identification of at-risk individuals. Current treatments for AD only provide symptomatic relief and do not alter the disease's progression. Cholinesterase inhibitors and NMDA antagonists are commonly used but do not prevent disease progression. Lifestyle modifications, such as diet and exercise, have shown some benefits in improving brain health and reducing AD risk. Research is focused on targeting AD's pathological features, including amyloid-beta (Aβ) and tau proteins. Several drugs have entered clinical trials but failed to demonstrate efficacy in late-stage trials. Other disease-modifying treatments targeting Aβ and tau pathologies, such as aducanumab and gantenerumab, are under investigation. Chaperones and natural extracts from Chinese medicine also show potential as AD treatments. Early administration of treatment and monitoring disease progression using biomarkers are crucial for successful AD management. Future therapies targeting tau pathology and combination therapies may slow AD progression. The development of potent and effective drugs for AD treatment is urgently needed.

9. Source of Funding

None.

10. Conflict of Interest

None.

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