WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 22, 216-231. Review Article ISSN 2277–7105

UNDERSTANDING NEURODEGENERATIVE DISEASES: A COMPLEX SPECTRUM OF AGE-RELATED DISORDERS

Pooja G. Gund*, Ajit B. Tuwar, Megha T. Salve

Student Miri, Pathardi, Ahmednagar Ahemdnagar Maharashtra India.

Article Received on
01 October 2024,

Revised on 21 October 2024,
Accepted on 11 Nov. 2024

DOI: 10.20959/wjpr202422-34514

***Corresponding Author**
Pooja G. Gund
Student Miri, Pathardi,
Ahmednagar Ahemdnagar
Maharashtra India.

ABSTRACT

Neurodegenerative diseases (NDDs) are a heterogeneous group of age-related disorders affecting millions worldwide, characterized by progressive neuronal loss in the central and peripheral nervous systems. These diseases, including Alzheimer's, Parkinson's, Huntington's, and others, are marked by the disruption of neural networks and the irreversible loss of terminally differentiated neurons. The increasing prevalence of NDDs, partly attributed to the growing elderly population, underscores the need for a deeper understanding of their underlying mechanisms. Oxidative stress, characterized by excessive reactive oxygen species (ROS) production, has been implicated in NDDs, highlighting the importance of exploring the intricate relationships between aging, neural degeneration, and ROS-mediated damage. This project aims to delve into the complexities of NDDs, shedding light on the pathophysiological processes underlying these devastating disorders and paving the way for the development of effective therapeutic strategies.

INTRODUCTION

Neurodegenerative diseases (NDDs) are a diverse group of neurological disorders that affect the lives of millions of people worldwide and cause progressive loss of neurons in the central nervous system (CNS) or peripheral nervous system.

Neurodegenerative diseases are age-related disorders classically characterized by progressive loss of structure or function of neurons and glial cells in the brain.

Disruption of the structure and function of neural networks and loss of neurons that cannot self-renew efficiently due to their terminally differentiated nature.

In recent years, these age-related diseases have become increasingly common, partly due to the increasing number of elderly people.

Neurodegenerative diseases include, for example, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and spinocerebellar ataxia.

Excessive production of reactive oxygen species (ROS) has also been associated with neurodegenerative diseases (ND), and therefore, many scientific works have been published on the influence of ROS in the development of common neurodegenerative diseases.

Continuous exposure to endogenous and environmental factors causes oxidative stress and DNA damage. Rare brain disorders caused by defects in DNA repair and DNA damage response (DDR) signaling demonstrate that failure to process DNA damage can lead to neurodegeneration.

The highly effective blood-brain barrier (BBB) continues to be a real obstacle for the successful management of MN.

As a suitable alternative to stop or reverse neurodegeneration, nanotherapies with the potential to cross the BBB (without damaging the barrier) have been proposed and demonstrated in many cases.

The use of nanotherapies is gaining ground due to numerous advantages over conventional dosage forms. Genetic changes are one of the main causes of these disorders. Certain proteins mutated in neurodegenerative diseases such as α-synuclein, presenilin-1, tau and huntingtin modulate brain plasticity and are usually located near membranes or participate in microtubule transport.

Despite the relentless efforts of modern science to create a medical or surgical solution, the results have not been favorable.

Neurons are highly susceptible to the accumulation of DNA damage due to their high energy requirements, high transcriptional activity and long lifespan. While more recent research has shown that DNA breaks and mutations can facilitate neuronal diversity during development and neuronal function throughout life, accumulating evidence indicates that the deterioration

of DNA damage to DNA repair is the cause of many neurological disorders, especially age-related neurodegenerative diseases.

These diseases are different in their pathophysiology – some cause memory impairment and cognitive impairment and others affect a person's ability to move, speak and breathe. The progressive loss of neurons, their structure and/or function, known as neurodegeneration.

The most common ND include Alzheimer's disease, Parkinson's disease, prion disease, amyotrophic lateral sclerosis, motor neuron disease, Huntington's disease, spinal muscular atrophy, and spinocerebellar ataxia. In the following sections, we will briefly discuss some common NDs.

Alzheimer's disease (AD)

Alzheimer's disease (AD) is one of the most common neurodegenerative disease and accounts for more than 80% of dementia cases worldwide in elderly people. It leads to the progressive loss of mental, behavioural, functional decline and ability to learn.

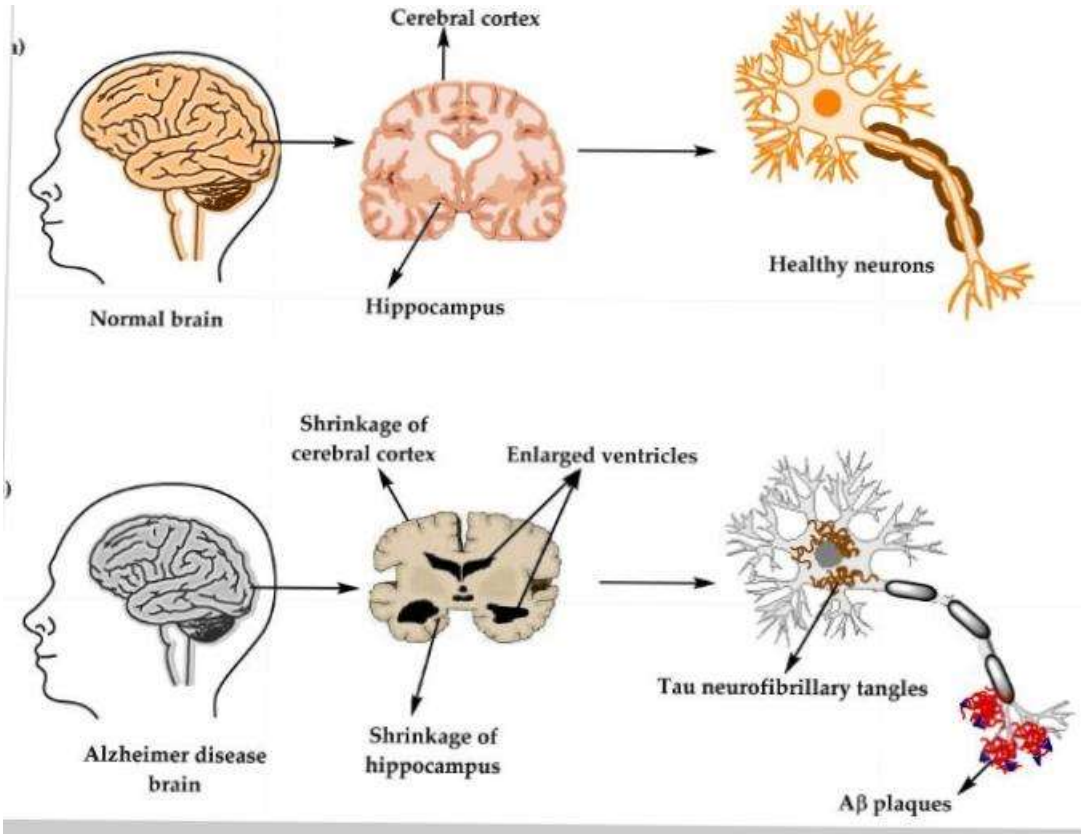
Alzheimer's disease (AD) (named after the German psychiatric Alois Alzheimer) is the most common type of dementia and can be defined as a slowly progressive neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles as a result of amyloid-beta peptide's (Aβ) accumulation in the most affected area of the brain, the medial temporal lobe and neocortical structures.

The most important risk factor for Alzheimer's disease is age, with the prevalence of the disease increasing exponentially after the age of 65. The overall prevalence of Alzheimer's disease is expected to double in 20 years with the increase in average life expectancy in developing countries.

Several risk factors for the development of Alzheimer's disease have been reported, including psychosocial, genetic and vascular parameters.

Vascular risk factors (for example, obesity, smoking and high blood cholesterol) and vascular disease (for example, diabetes mellitus, hypertension and stroke) are associated with an increased risk of the disease of Alzheimer's. Psychosocial factors, such as low education, lack of social engagement, and weak social networks are also associated with an increased risk of Alzheimer's disease.

The progressive loss of cognitive functions can be caused by a brain disorder such as Alzheimer's disease (AD) or other factors, such as poisoning, infections, abnormalities of the pulmonary and circulatory systems, which lead to reduction of the supply of oxygen to the heart. . Brain, food. Deficiency, lack of vitamin B12, tumors and others.



Alzheimer's disease diagnostic criteria

Patient who is suspected of having Alzheimer's disease should undergo several tests, including a neurological examination, magnetic resonance imaging (MRI) of neurons, laboratory tests such as vitamin B12 and other tests, plus the history medical and family of patients. According to several studies, vitamin (vit.) B12 deficiency has long been known to be associated with neurological problems and an increased risk of Alzheimer's disease.

Vitamin (vit.) B12 deficiency has long been known to be associated with neurological problem.

Alzheimer's Disease's Neuropathology

There are two types of neuropathological changes in AD that provide evidence of disease progression and symptoms and include: (1) positive lesions (due to accumulation), which are characterized by the accumulation of aggregates of neurofibrillary deposits, plaque amyloid,

dystrophic neurites. , neuropilar fibers and other deposits found in the brains of AD patients. In addition to (2) negative lesions (due to losses), which are characterized by significant atrophy due to neuronal, neuropilar and synaptic loss.

In addition, other factors can cause neurodegeneration such as neuroinflammation, oxidative stress, and damage to cholinergic neurons.

The Stages of Alzheimer's Disease

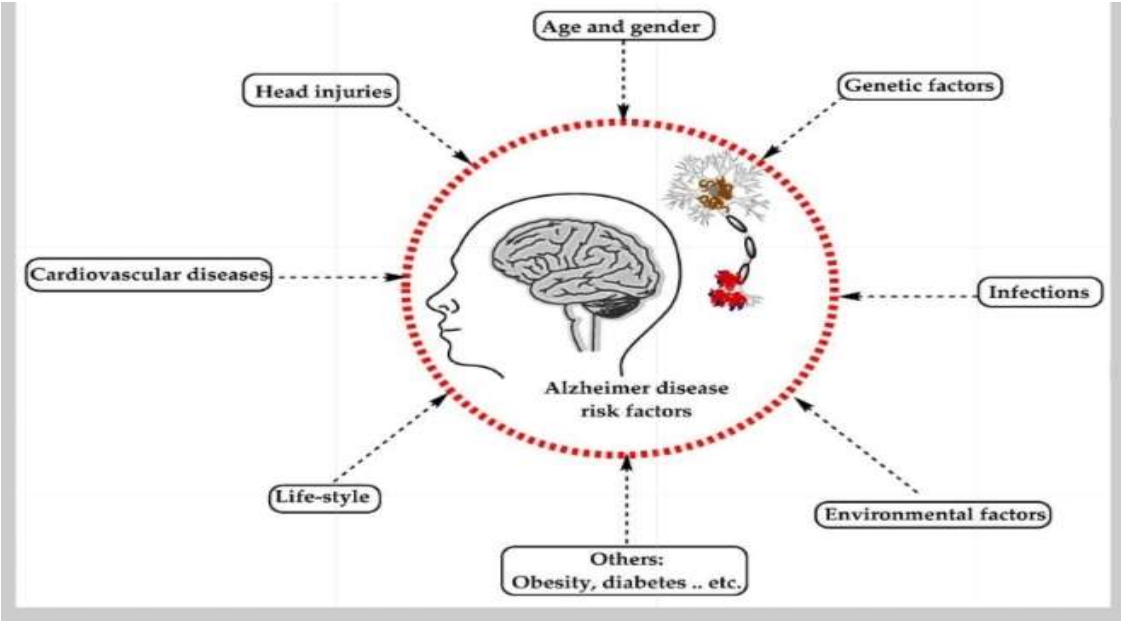
The clinical stages of Alzheimer's disease can be classified 4 stages

(1) The preclinical or presymptomatic stage, which can last for several years or more. This stage is characterized by mild memory loss and early pathological changes in the cortex and hippocampus, without functional alteration of daily activities and the absence of clinical signs and symptoms of Alzheimer's disease.

(2) The mild or initial stage of Alzheimer's disease, where patients begin to see several symptoms, such as disturbance in the patient's daily life with loss of concentration and memory, disorientation of place and time, mood changes and the development of depression.

(3) The moderate stage of Alzheimer's disease, in which the disease spreads to areas of the cerebral cortex, causing increasing memory loss with difficulty recognizing family and friends, loss of control over the impulse, and the difficulty of reading, writing and speaking.

(4) Alzheimer's disease in the late stage, which involves the spread of the disease throughout the cortical area with a severe accumulation of senile plaques and neurofibrillary tangles, leading to progressive functional and cognitive impairment where patients cannot not recognize his family at all and, finally, lead to death. Of the patient because of these complications.



Causes and Risk Factors of Alzheimer's Disease

AD is considered a multifactorial disease associated with several risk factors, such as advanced age, genetic factors, head trauma, vascular disease, infections and environmental factors (heavy metals, trace metals and others).

Alzheimer's disease is a disease whose detailed pathogenesis is not crystal clear. The pathology of Alzheimer's disease is characterized by two basic features. First, the collection of fragments, for example. Aβ plaques, found in the outer membrane of neurons. In addition, twisted strands of tau protein, called tangle tangles, are present in the cytosol of neurons. Several hypotheses regarding the pathology of Alzheimer's disease have been reported, as explained below.

1) Cholinergic deficiency

During the progression of AD, cholinergic neurons in the basal forebrain are severely damaged. Histopathologically, a decrease in the number of neurons and marker enzymes responsible for the synthesis and degradation of acetylcholine (Ach) is observed. Neurochemically, this cholinergic brain deficit leads to memory loss and other cognitive and non-cognitive symptoms characteristic of AD. Cholinergic dysfunction is a recognized feature of AD; however, cholinesterase inhibitors Such as donepezil, galantamine and rivastigmine only alleviate the symptoms but not the progression of AD. These clinical observations indicate that cholinergic imbalance may simply be a clinical feature of AD. Basic treatment requires a better understanding of the etiology of AD.

2) Cholesterol

Cholesterol regulates the production and elimination of Aβ. A variant of the apolipoprotein E (APOE) gene is consistent with the role of cholesterol in the pathogenesis of AD and has been identified as a major genetic risk factor for AD. Numerous in vitro and in vivo studies in AD have shown that high cholesterol levels accelerate Aβ formation. Intracellular cholesterol is also involved in the regulation of APP processing by directly modifying secretase activity.

3) Inflammation

Neuroinflammation in AD involves inflammatory components, complement activation pathways, and other receptors on brain cells, such as microglia and astrocytes.[46] Aβ can stimulate microglia and astrocytes to express major histocompatibility complex II (MHC II) and increase the secretion of interleukins, prostaglandins, leukotrienes, thromboxanes, coagulation factors and protease inhibitors. These responses orchestrate the inflammatory response in AD patients.

Therapeutic approaches for AD

The therapeutic approach for the management of AD focuses mainly on the different pathways of disease progression. Currently, there are three classes of drugs approved by the US FDA for the management of AD, each of which is described below.

3.1.1. Antibodies that target beta-amyloid (Aβ) plaques

Aducanumab (Aduhelm) is the first disease-modifying drug approved for AD patients and was approved in June 2021. It is administered as an intravenous (IV) infusion over approximately one hour every four weeks. Aducanumab is an IgG1 monoclonal antibody specific for extracellular Aβ plaques in the brain, which binds to the plaques and helps clear them. Although it has been conditionally approved, clinical data for aducanumab show a reduction in Aβ plaque burden, but without any association with an improvement in cognitive functions in patients. Further clinical data will also be collected to provide definitive evidence of the drug's effectiveness on cognitive functions. However, the approval of aducanumab also created a wave of enthusiasm among Alzheimer's patients and advocacy groups. In addition to being the first therapy aimed at modifying the pathology of the In addition to being the first therapy aimed at modifying the pathology of the disease, they believe that it will pave the way for similar therapies in the near future.

Several clinical trials using different bioactive molecules (ie, secretase inhibitors and therapeutic antibodies) have been conducted, but most of them have been completed to date. Several antibodies targeting Aβ, AAB-003, MEDI1814, RO7126209 and SAR228810, have completed phase I clinical trials. Although aducanumab has completed phase III clinical trials, it is also specific for Aβ aggregation. Similarly, antibodies specific for tau or TREM 2, i.e. BIIB076, bepranemab, JNJ-63733657, have ended Phase I clinical trial, while gosuranemab is in phase 2 clinical trial. Thus, other antibody-based drugs may soon receive FDA approval for the treatment of AD.

3.1.2. Cholinesterase inhibitors

Currently, cholinesterase inhibitors are the first-line drugs administered for AD. Donepezil, rivastigmine and galantamine are the three main cholinesterase inhibitors in clinical use. AD is associated with a loss of cholinergic neurons and a decrease in the amount of acetylcholine in the cortical regions of the brain. Many studies have found that increasing the intake of acetylcholine in dementia patients helps reduce cognitive decline. Limit of cholinesterase inhibitors Breakdown of acetylcholine and the patient benefits from increased cholinergic activity.

Tacrine was the first cholinesterase inhibitor approved in 1993 by the FDA, but its use was later abandoned due to its associated hepatotoxicity. Donepezil is used for mild to moderate atopic dermatitis and is administered as oral tablets of 5 or 10 mg/day. Recently, higher doses of donepezil (23 mg/day), alone or in combination with memantine, have been approved for patients with moderate to severe atopic dermatitis. Another acetylcholinesterase inhibitor used for mild to moderate atopic dermatitis is rivastigmine. Unlike other cholinesterase inhibitors, rivastigmine is available as a transdermal patch and inhibits the enzymes acetylcholinesterase and butyrylcholinesterase. Galantamine, another class of cholinesterase inhibitors, is approved for mild to moderate AD at a dose between 16 and 24 mg/day. In addition to its inhibitory effect on cholinesterase activity, it also produces an allosteric modulation of nicotinic cholinergic receptors.

Although many drugs have been developed for Alzheimer's disease, cholinesterase inhibitors remain the only option available to patients. Aducanumab, a recently approved drug, is controversial for its effectiveness and its price is excessive. However, cholinesterase inhibitors have limited efficacy. They provide only a modest improvement in the cognitive

abilities of patients and are considered symptomatic treatment options rather than pathology modification. Also, it is debatable whether current medications can.

Effectively cross the BBB in large doses to produce the desired pharmacological effects.

3.1.3. Glutamate regulators

Glutamate is the main excitatory neurotransmitter in the brain. Due to excessive activation of postsynaptic neurons, such as NMDA receptors, glutamates cause neuronal damage, leading to neurodegeneration. However, complete inhibition of NMDA receptors resulted in serious effects. Therefore, memantine was developed, a non-competitive NMDA receptor antagonist, which provides pathological benefits with NMDA receptor activation and also protects patients from the inhibitory effects due to Hyperactivation.

Current therapeutic approaches for the treatment of ND

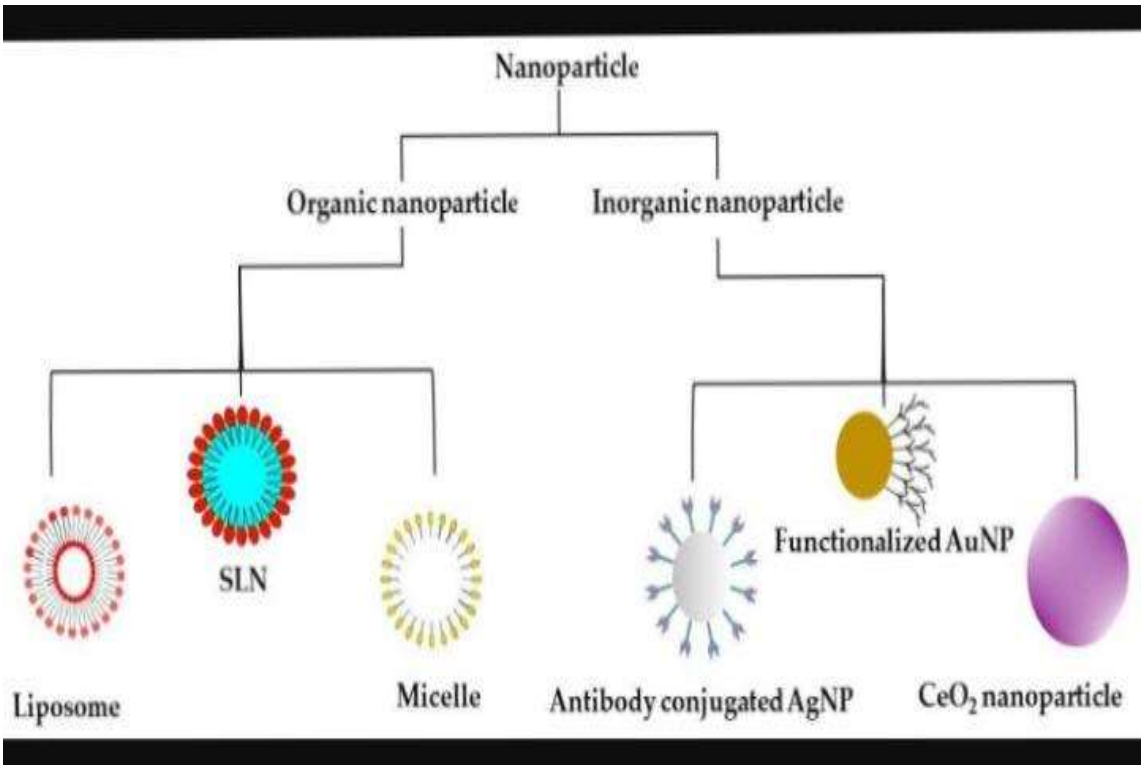
Degenerative diseases of the nervous system represent a significant medical and public health burden for populations around the world. Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) are three of the major neurodegenerative diseases. The prevalence and incidence of these diseases increases significantly with age; Therefore, the number of cases is expected to increase in the foreseeable future, as life expectancy in many countries continues to increase. The causal contributions of genetic and environmental factors are, with few exceptions, poorly understood. However, molecular epidemiology approaches have proven valuable for improving disease diagnoses, characterizing disease prognostic factors, identifying high-risk genes for familial neurodegenerative diseases, studying common genetic variants that can predict the susceptibility to non-disease forms of the family history of these diseases exposure. Management of neurodegenerative disorders is often disease specific. Different management approaches are currently accepted, which aim at the pathogenesis of the disease or attempt to improve the symptoms experienced. In this review, we review the therapeutic approaches currently in practice to treat major neurodegenerative disorders.

Nanoparticles and Their use in ND

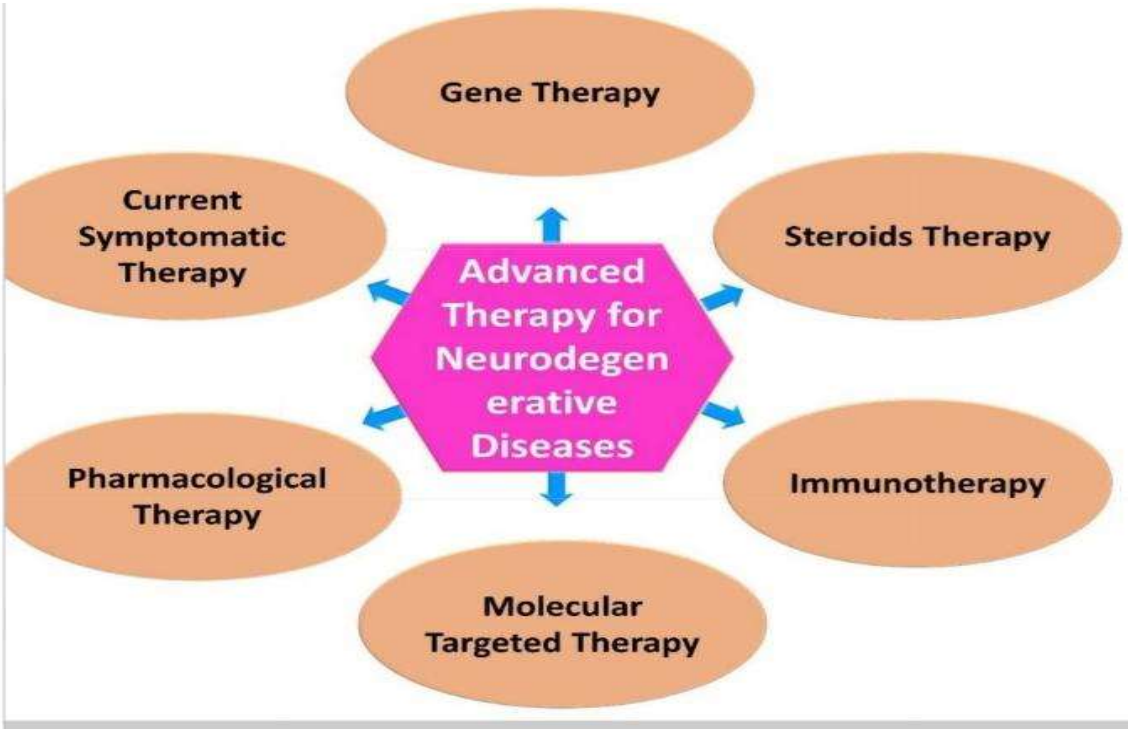
The limitations caused by the BBB and the shortcomings of current therapies, as mentioned above, have led to an unmet need for new therapeutic approaches for the treatment of ND. Among the approaches used, nanotechnology has emerged as a safe and promising platform for the delivery of targeted drugs/genes to the CNS. This technology uses nanoscale

materials, typically between 1 and 1000 nm, and can interact with biological systems at the molecular level. A variety of materials such as.

Natural polymers (Proteins and Polysaccharides), synthetic polymers (PLGA and PCL) and inorganic materials (gold, silver and cerium) have been used to formulate nanoparticles. Nanocarriers have been shown to be very suitable drug/gene carriers in the brain. The characteristics of nanocarriers that make them a promising platform for the management and treatment of ND include high drug loading capacity, low systemic toxicity, increased drug permeability and good physical and chemical stability. Nanoparticles of different sizes, properties and functions have been developed to deliver drugs to the brain. However, their penetration through the BBB depends on the size, surface chemistry, type and polarity of the nanocarriers. In addition, polysorbate surface coating can help to avoid transmembrane efflux systems, such as liposomal polymer particle pumps and P-glycoprotein, which have been most exploited for targeted delivery to the brain due to ease of surface modification. Cell Penetrating Peptides and Ligands (CPPs)



Some advanced therapies for neurodegenerative disease



1) Gene therapy

Gene therapy for neurodegenerative diseases: Gene therapy is considered a promising approach for the treatment of neurodegenerative diseases. This involves understanding the mechanisms of these diseases that regulate gene expression at specific times and places in order to develop effective treatments. Challenges of gene therapy: One of the main challenges is the prevention of the escape of the therapeutic genes in the neighboring regions or the surrounding blood vessels. This leak can reduce the effectiveness of Therapy and cause unwanted effects.

The process of transduction: Gene therapy involves the delivery of therapeutic genes to target cells or tissues. The process of introducing these genes into the target cells is called transduction.

Real-time monitoring: Real-time monitoring of the administration of these therapeutic genes has become a common practice. This is often done with iMRI-CED (iMRI-CED), which helps ensure that the genes are delivered precisely to the target area.

Clinical trials: If this advanced neurosurgical technique is successfully implemented, it could help translate promising preclinical therapies for neurodegenerative disorders into clinical trials, potentially leading to new treatments for these diseases.

Gene therapy has great potential to treat neurodegenerative diseases by correcting genetic disorders, providing therapeutic effects.

2) Immunotherapy

Aging-related neurodegenerative diseases and non-autoimmune diseases represent an important health challenge, but have received relatively limited attention in the context of immunotherapies. Although immunotherapies have shown promise for autoimmune disorders, their potential in these specific neurodegenerative diseases remains largely untapped. The complex nature of these diseases, involving multiple pathological mechanisms and complex interactions between aging, neuroinflammation, and neuronal dysfunction, presents unique challenges for immunotherapy development.

Recent advances in the immunomodulation of the central nervous system have allowed us to better understand its functioning. The exploration of new targets for immunotherapy strategies is an important path of research in the field of medicine. While classic disease biomarkers have proven valuable for diagnostic and therapeutic purposes, the identification and targeting of new immune-related targets may provide additional opportunities for the development of innovative immunotherapies. The possibility of further treatment.

Effective treatment appears to be found in immunotherapy targeting abnormal protein aggregates or inflammatory molecules.

3) Pharmacological therapy

Pharmacological therapy of particular interest are anti-beta-amyloid, nerve growth factor and anti-inflammatory properties of drugs being studied or awaiting approval for the treatment of Alzheimer's disease. By modulating secretase activity and increasing the synthesis of beta-amyloid precursor proteins, some drugs inhibit beta-amyloid production in addition to acetylcholinesterase. In addition to immunotherapy, the interaction of metal ions with beta-amyloid and oxidative reactions, as well as metabolic and hormonal control can be monitored. Several dopamine uptake inhibitors and AMPA glutamate receptor antagonists are expected to be registered for the treatment of Parkinson's disease symptoms.

Pharmacological therapy Of particular interest are anti-beta-amyloid, nerve growth factor and anti-inflammatory properties of drugs being studied or awaiting approval for the treatment of Alzheimer's disease. By modulating secretase activity and increasing the synthesis of beta-amyloid precursor proteins, some drugs inhibit beta-amyloid production in addition to acetylcholinesterase. In addition to immunotherapy, the interaction of metal ions with beta-amyloid and oxidative reactions, as well as metabolic and hormonal control can be monitored. Several dopamine uptake inhibitors and AMPA glutamate receptor antagonists are expected to be registered for the treatment of Parkinson's disease symptoms.

REFERENCE

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5451177/
2. Gitler, A. D., Dhillon, P., & Shorter, J. Neurodegenerative disease: models, mechanisms, and a new hope. Disease Models & Mechanisms, 2017; 10(5): 499–502. https://doi.org/10.1242/dmm.030205
3. Gitler, A. D., Dhillon, P., & Shorter, J. Neurodegenerative disease: models, mechanisms, and a new hope. Disease Models & Mechanisms, 2017; 10(5): 499–502. https://doi.org/10.1242/dmm.030205
4. Gitler, A. D., Dhillon, P., & Shorter, J. Neurodegenerative disease: models, mechanisms, and a new hope. Disease Models & Mechanisms, 2017; 10(5): 499–502. https://doi.org/10.1242/dmm.030205
5. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=research+topic+neurodegenerative+diseases&oq=#d=gs_qabs&t=1729821952229&u=%23p%3DIxuh8m8IDbcJ
6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8837071/#ref-list-a.l.htitle
7. Harilal S., Jose J., Parambi D.G.T., Kumar R., Mathew G.E., Uddin M.S., Kim H., Mathew B. Advancements in nanotherapeutics for Alzheimer's disease: Current perspectives. J. Pharm. Pharmacol, 2019; 71: 1370–1383. Doi: 10.1111/jphp.13132. [DOI] [PubMed] [Google Scholar]
8. Hinge N.S., Kathuria H., Pandey M.M. Engineering of structural and functional properties of nanotherapeutics and nanodiagnostics for intranasal brain targeting in Alzheimer's. Appl. Mater. Today, 2022; 26: 101303. Doi: 10.1016/j.apmt.2021.101303. [DOI] [Google Scholar]
9. Aaron D. Gitler, Paraminder Dhillon, James Shorter neurodegenerative disease models mechanism and new hope Dis Model Mech, 2017; 1, 10(5): 499–502. Doi: 10.1242/dmm.030205

10. Martin J.B. Molecular basis of the neurodegenerative disorders. N. Engl. J. Med, 1999; 340: 1970–1980. Doi: 10.1056/NEJM199906243402507.
11. Hague S., Klaffke S., Bandmann O. Neurodegenerative disorders: Parkinson's disease and Huntington's disease. J. Neurol. Neurosurg. Psychiatry, 2005; 76: 1058–1063. Doi: 10.1136/jnnp.2004.060186. [DOI] [PMC free article] [PubMed] [Google Scholar]
12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7764106/
13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7764106/
14. Therapeutics of Alzheimer's disease: past, present and future Neuropharmacology. Neuropharmacology, 2014.
15. Terry, R. D., & Davies, P. Dementia of the Alzheimer type. Annual Review of Neuroscience, 1980; 3(1): 77–95. https://doi.org/10.1146/annurev.ne.03.030180.000453
16. De-Paula, V. J., Radanovic, M., Diniz, B. S., & Forlenza, O. V. Alzheimer's disease. In Subcellular Biochemistry, 2012; 329–352. Springer Netherlands.
17. Rathmann, K. L., & Conner, C. S. Alzheimer's disease: Clinical features, pathogenesis, and treatment. Drug Intelligence & Clinical Pharmacy, 1984; 18(9): 684–691. https://doi.org/10.1177/106002808401800902
18. Schachter, A. S., & Davis, K. L. Alzheimer's disease. Current Treatment Options in Neurology, 2000; 2(1): 51–60. https://doi.org/10.1007/s11940-000-0023-0
19. Cho, H. S., Huang, L. K., Lee, Y. T., Chan, L., & Hong, C. T. Suboptimal baseline serum vitamin B12 is associated with cognitive decline in people with Alzheimer's disease undergoing cholinesterase inhibitor treatment. Frontiers in Neurology, 2018; 9. https://doi.org/10.3389/fneur.2018.00325
20. Cho, H. S., Huang, L. K., Lee, Y. T., Chan, L., & Hong, C. T. Suboptimal baseline serum vitamin B12 is associated with cognitive decline in people with Alzheimer's disease undergoing cholinesterase inhibitor treatment. Frontiers in Neurology, 2018; 9. https://doi.org/10.3389/fneur.2018.00325
21. Singh, S. K., Srivastav, S., Yadav, A. K., Srikrishna, S., & Perry, G. Overview of Alzheimer's disease and some therapeutic approaches targeting Aβ by using several synthetic and herbal compounds. Oxidative Medicine and Cellular Longevity, 2016; (1). https://doi.org/10.1155/2016/7361613
22. Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., Bakardjian, H., Benali, H., Bertram, L., Blennow, K., Broich, K., Cavedo, E., Crutch, S., Dartigues, J.-F., Duyckaerts, C., Epelbaum, S., Frisoni, G. B., Gauthier, S., Genthon, R., … Proceedings of the Meeting of the International Working Group (IWG) and the American

Alzheimer's Association on "The Preclinical State of AD"; July 23, 2015; Washington DC, USA. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 2016; 12(3): 292–323. https://doi.org/10.1016/j.jalz.2016.02.002

23. De-Paula, V. J., Radanovic, M., Diniz, B. S., & Forlenza, O. V. Alzheimer's disease. In Subcellular Biochemistry, 2012; 329–352. Springer Netherlands.
24. A. Armstrong, R. Risk factors for Alzheimer's disease. Folia Neuropathological, 2019; 57(2): 87–105. https://doi.org/10.5114/fn.2019.85929
25. Dunn B., Stein P., Cavazzoni P. Approval of Aducanumab for Alzheimer Disease—The FDA's Perspective. JAMA Intern. Med, 2021; 181: 1276–1278. doi: 10.1001/jamainternmed.2021.4607
26. Jain N., Chen-Plotkin A.S. Genetic modifiers in neurodegeneration. Curr. Genet. Med. Rep, 2018; 6: 11–19. Doi: 10.1007/s40142-018-0133-1.
27. Hampel, H., Mesulam, M.-M., Cuello, A. C., Khachaturian, A. S., Vergallo, A., Farlow, M. R., Snyder, P. J., Giacobini, E., & Khachaturian, Z. S. Revisiting the Cholinergic Hypothesis in Alzheimer's disease: Emerging evidence from translational and clinical research. The Journal of Prevention of Alzheimer's Disease, 2018; 1–14. https://doi.org/10.14283/jpad.2018.43
28. Deardorff W.J., Feen E., Grossberg G.T. The use of cholinesterase inhibitors across all stages of Alzheimer's disease. Drugs Aging, 2015; 32: 537–547. Doi: 10.1007/s40266-015-0273-x.
29. Arora, S., Sharma, D., & Singh, J. GLUT-1: An effective target to deliver brain-derived neurotrophic factor gene across the blood brain barrier. ACS Chemical Neuroscience, 2020; 11(11): 1620–1633. https://doi.org/10.1021/acschemneuro.0c00076
30. Cano A., Sánchez-López E., Ettcheto M., López-Machado A., Espina M., Souto E.B., Galindo R., Camins A., García M.L., Turowski P. Current advances in the development of novel polymeric nanoparticles for the treatment of neurodegenerative diseases. Nanomedicine, 2020; 15: 1239–1261. Doi: 10.2217/nnm-2019-0443. [DOI] [PubMed] [Google Scholar]
31. https://pmc.ncbi.nlm.nih.gov/articles/PMC10405853/
32. Liu, D., Zhang, Q., Luo, P., Gu, L., Shen, S., Tang, H., Zhang, Y., Lyu, M., Shi, Q., Yang, C., & Wang, J. Neuroprotective effects of celastrol in neurodegenerative diseases-unscramble its major mechanisms of action and targets. Aging and Disease, 2022; 13(3): 815–836. https://doi.org/10.14336/AD.2021.1115

33. Krzysztoforska, K., Mirowska-Guzel, D., & Widy-Tyszkiewicz, E. Pharmacological effects of protocatechuic acid and its therapeutic potential in neurodegenerative diseases: Review on the basis of in vitro and in vivo studies in rodents and humans. Nutritional Neuroscience, 2019; 22(2): 72–82. https://doi.org/10.1080/1028415x.2017.1354543