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Neurodegenerative Disorders: Mechanisms of Degeneration and Therapeutic Approaches with Their Clinical Relevance

Dnyandev G. Gadhave[1,2#], Vrashabh V. Sugandhi[1,2#], Saurav Kumar Jha[3], Sopan N. Nangare[4], Gaurav Gupta[5,6,7], Sachin Kumar Singh[8,7], Kamal Dua, Hyunah Cho[2,***], Philip M Hansbro[5,**], Keshav Raj Paudel[5,*]

[1]Department of Pharmaceutics, Dattakala Shikshan Sanstha's, Dattakala College of Pharmacy (Affiliated to Savitribai Phule Pune University), Swami Chincholi, Daund, Pune 413130, Maharashtra, India

[2]College of Pharmacy & Health Sciences, St. John's University, 8000 Utopia Parkway, Queens, NY, 11439, USA

[3]Department of Biological Sciences and Bioengineering (BSBE), Indian Institute of Technology, Kanpur, 208016, Uttar Pradesh, India

[4]Department of Pharmaceutics, H. R. Patel Institute of Pharmaceutical Education and Research, Shirpur: 425405, Dist- Dhule (MS), India

[5]School of Pharmacy, Suresh Gyan Vihar University, Jagatpura 302017, Mahal Road, Jaipur, India

[6]Centre for Transdisciplinary Research, Saveetha Institute of Medical and Technical Science, Saveetha University, Chennai, India

[7]School of Pharmacy, Graphic Era Hill University, Dehradun 248007, India

[8]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara-144411, India

[9]Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, NSW 2007, Australia

[10]Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Ultimo, NSW 2007, Australia

[11]Centre for Inflammation, Faculty of Science, School of Life Science, Centenary Institute and University of Technology Sydney, Sydney, 2007, Australia

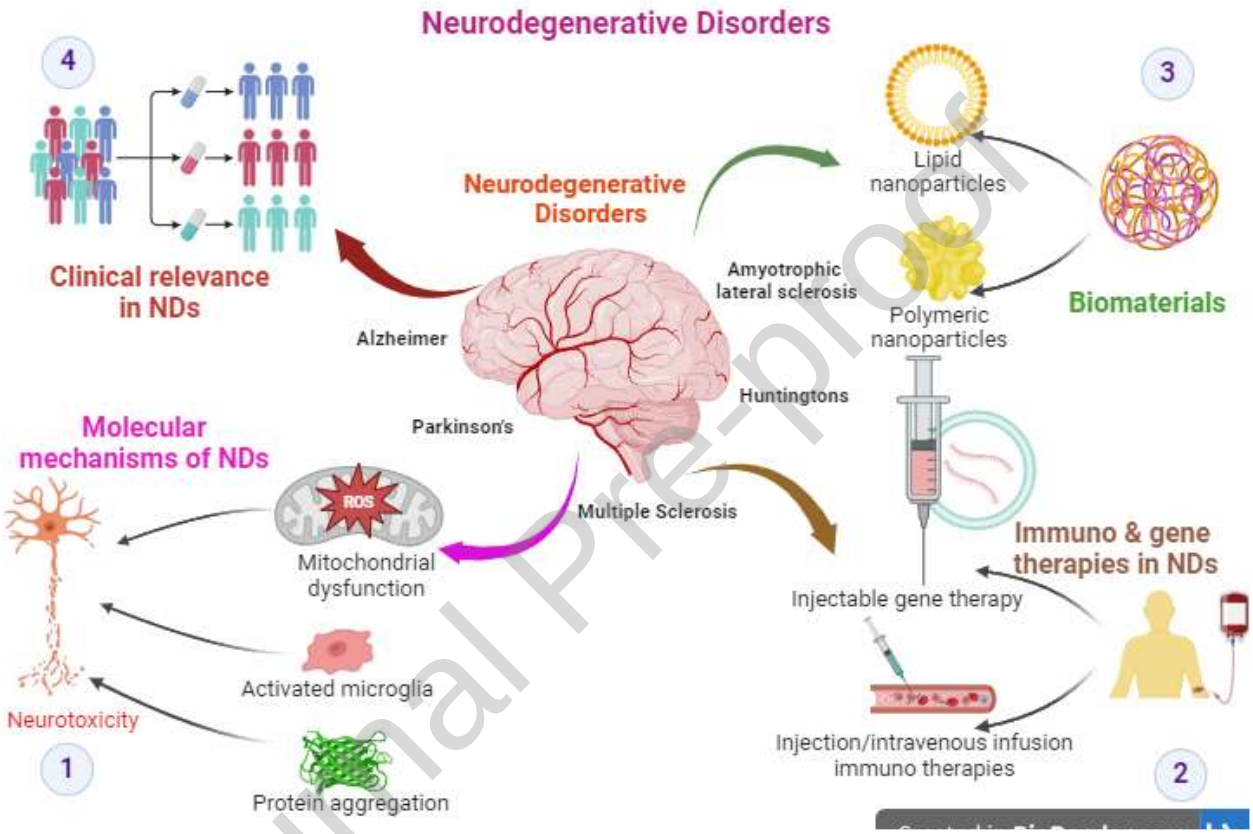
Corresponding authors:

*Dr. Keshav Raj Paudel (Keshavraj.paudel@uts.edu.au) and **Prof Philip M. Hansbro (Philip.hansbro@uts.edu.au), Centre for Inflammation, Faculty of Science, School of Life Science, Centenary Institute and University of Technology Sydney, Sydney, 2007, Australia.

***Assistant Prof. Hyunah Cho, College of Pharmacy & Health Sciences, St. John's University, 8000 Utopia Parkway, Queens, NY, 11439, USA

# Both authors contributed equally

Graphical abstract



Abstract

Neurodegenerative disorders (NDs) are expected to pose a significant challenge for both medicine and public health in the upcoming years due to global demographic changes. NDs are mainly represented by degeneration/loss of neurons, which is primarily accountable for severe mental illness. This neuronal degeneration leads to many neuropsychiatric problems and permanent disability in an individual. Moreover, the tight junction of the brain, blood-brain barrier (BBB)has a protective feature, functioning as a biological barrier that can prevent medicines, toxins, and foreign substances from entering the brain. However, delivering any medicinal agent to the brain in NDs (i.e., Multiple sclerosis, Alzheimer's, Parkinson's, etc.) is enormously challenging. There are many approved therapies to address NDs, but most of them only help treat the associated manifestations. The available therapies have failed to control the progression of NDs due to certain factors, i.e., BBB and drug-associated undesirable effects. NDs have extremely complex pathology, with many pathogenic mechanisms involved in the initiation and progression; thereby, a limited survival rate has been observed in ND patients. Hence, understanding the exact mechanism behind NDs is crucial to developing alternative approaches for improving ND patients' survival rates. Thus, the present review sheds light on different cellular mechanisms involved in NDs and novel therapeutic approaches with their clinical relevance, which will assist researchers in developing alternate strategies to address the limitations of conventional ND therapies. The current work offers the scope into the near future to improve the therapeutic approach of NDs.

Keywords: Neurodegenerative disorders; Cellular mechanisms of neurodegeneration; Blood-brain barrier; Novel therapeutic approaches; Biomaterials.

1. Introduction

Neurodegenerative disorders (NDs) are marked by a deliberate loss of neurons, usually leading to death (Gadhave et al., 2024; Lamptey et al., 2022a). These include progressive neuropsychiatric conditions, such as Alzheimer's disease (AD), Multiple sclerosis (MS), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and various other NDs (Choonara et al., 2009; Hui et al., 2023). NDs are commonly associated with gradually losing neurons and synaptic connections, typically occurring in later life (Pant et al., 2022; Tanaka et al., 2020). Specific diseases are distinguished by characteristic symptoms that depend on the location of neuronal loss in the brain (**Fig. 1A**) (Gadhave et al., 2024). Diagnosis of NDs depends on the clinical prevalence of the patient and supportive evidence from magnetic resonance imaging (MRI) (Huang and Zhang, 2023). The degree of neuronal loss directly correlates with the appearance and progression of clinical symptoms. In ADs, neuronal loss appears early in the hippocampus, a brain region involved in declarative episodic memory (Jiménez-Balado and Eich, 2021; Shankar and Walsh, 2009). In PD, the typical clinical trial for assessing tremor, bradykinesia, and postural instability can only detect these after a significant loss of 70-80% of dopaminergic neurons in the substantia nigra (Clarke, 2008; DeMaagd and Philip, 2015). However, in MS, the activated immune responses (microglia) attack the myelin sheaths of neurons, leading to demyelination and causing difficulty in neuronal signal conduction. Further, they are responsible for various mental problems (Gadhave et al., 2024; Gadhave and Kokare, 2019).

According to previous investigations, NDs are reported to have a limited survival rate. Most recently, in 2019, a total of 10 million deaths and 349.2 million individuals were affected by major neurological disorders worldwide (Ding et al., 2022; Huang et al., 2023). These disorders ranked second in terms of global prevalence. **Fig. 1B.** summarizes the incidence, prevalence, and impact associated with major NDs ("Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019," 2022). Among these disorders, AD accounted for the highest number of deaths, followed by neonatal dementia and memory loss (Castelpietra et al., 2022). AD is noted as the 6th leading cause of death worldwide, with 121,499 deaths in 2019 ("2023 Alzheimer's disease facts and figures," 2023). Moreover, > 55 million individuals have

dementia globally, and around 60% of patients belong to low-and middle-income nations (Naheed et al., 2023). Similarly, in 2019, the global prevalence of PD exceeded 8.5 million people; recent estimations indicate that PD led to 5.8 million disability-adjusted lives, reflecting an 81% surge since 2000 (Ou et al., 2021). Moreover, PD was responsible for 329,000 deaths, marking a staggering increase of over 100% since 2000. A global preponderance of MS is believed to exceed 1.8 million individuals. In the year 2019, there were 59,345 newly diagnosed cases of MS and 22,439 deaths worldwide (Wallin et al., 2019). The occurrence, mortality, and disability-adjusted lives associated with MS have been steadily increasing over time, while the age-standardized rates have experienced a slight decline from 1990 to 2019 (Gadhave et al., 2024). The global estimates of ALS are between 1.9 and 6 cases per 100,000 people. A total of 24,328 ALS deaths were recorded (Arthur et al., 2016), leading to an age-adjusted mortality rate of 1.70 (Larson et al., 2018). Previous epidemiological reports on HD have exhibited a combined occurrence rate of 0.38 cases per 100,000 individuals yearly and a worldwide presence of 2.71 cases per 100,000 people yearly (Kim et al., 2015). Additionally, 2.27 individuals per million population die annually as a result of HD. **Fig. 1C&D** represented the statistics of mortality and severity/prevalence caused due to major NDs. However, NDs are more prevalent in the aged population, and the risk of developing NDs depends on different factors and genetic conditions (Lamptey et al., 2022a).

Currently, there are many approved therapies to address NDs, but most of them only help treat the associated manifestations (Dnyandev Gadhave et al., 2023). The available therapies have failed to control the progression of NDs due to different challenges associated with NDs therapies, such as the blood-brain barrier (BBB) and many unwanted side effects of available treatments, which leads to a lower survival rate (D. Gadhave et al., 2023, 2019; Niazi, 2023). Numerous researchers have emphasized nanoscale strategies that could be utilized to treat CNS disorders such as NDs (Gadhave et al., 2021). According to several recent articles, biomaterials have the potential to be highly selective and effective in facilitating molecular detection as well as targeted drug delivery, therapeutic monitoring, and diagnosis of NDs (Gadhave et al., 2021, 2018; D. G. Gadhave et al., 2019). Furthermore, a better understanding of the precise mechanisms of NDs initiation may help discover new treatment options, increasing the prospects for better treatments.

The current review focuses on the shortcomings of traditional treatments, understanding the exact mechanism of NDs initiation, the progress of biomaterials in treating NDS, and their clinical relevance, which opens new possibilities for improving the therapeutic aspects of NDs shortly.

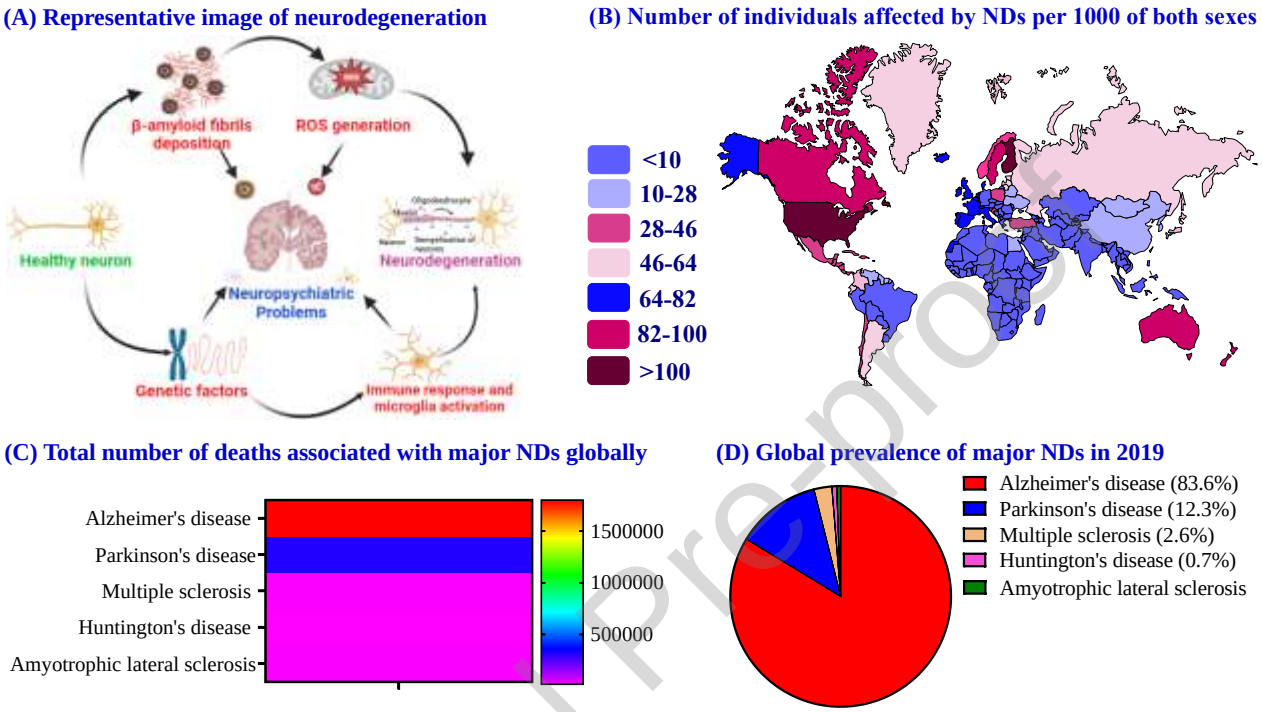


Fig. 1: (A) Representative image of neurodegeneration; (B) Map displaying regional differences in NDs prevalence and the number of people affected by NDs per 100000 people by nation. As per the key, scores of <10, 10-28, 28-46, 46-64, 64-82, 82-100 and > 100 people affected amongst 100000 are exhibited in varying colors. (C) A statistical representation of the total number of deaths due to major NDs globally. (D) Statistical representation on % global prevalence of major NDs in 2019.

2. Major Types of Neurodegenerative Disorders (NDs)

2.1 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, immune-mediated neurological disorder that affects the central nervous system (CNS), which includes the brain and spinal cord (Fig. 2). MS is characterized by the immune system mistakenly attacking myelin, a protective covering around nerve fibers (Goldenberg, 2012) (Lamptey et al., 2022b). This leads to inflammation, demyelination, and damage to the underlying neurons. This disrupts the normal propagation of electrical impulses along the nerves. The manifestations of MS can vary considerably and encompass fatigue, compromised mobility, sensory anomalies such as numbness or tingling, muscular debility, coordination deficiencies, visual disruptions including blurred or double vision, and cognitive impairments affecting memory and concentration (Coles, 2015). There are three distinct classifications of MS: Relapsing-remitting MS (RRMS) is defined by alternating episodes of relapses or flare-ups and subsequent periods of partial or complete recovery. Primary Progressive MS (PPMS) is characterized by a continuous progression of disability from the beginning, without distinct relapses or remissions (Klineova and Lublin, 2018). Lastly, secondary progressive MS (SPMS) initially presents as RRMS but later transitions into a progressive phase with deteriorating symptoms and disability. The exact cause of MS is still uncertain; nevertheless, it is believed to arise from an intricate interaction between genetic and environmental factors. Potential risk factors include certain illnesses, inadequate vitamin D levels, and smoking (Sugandhi et al., 2024). The diagnosis of MS may be challenging owing to the lack of a definitive diagnostic test. Neurologists often rely on a combination of clinical history, physical examination, MRI scans, and sometimes even analysis of spinal fluid to make a diagnosis (Ömerhoca et al., 2018). Currently, there is no recognized cure for MS. Nevertheless, there are several therapeutic strategies that focus on symptom management, altering the course of the disease, and enhancing the general well-being of MS sufferers. Pharmaceuticals, therapeutic activities, and lifestyle modifications are often used. The development of MS varies significantly across individuals. Some people may have mild symptoms and have long periods without symptoms, while others may have a slower and more debilitating decline. The current research primarily focuses on comprehending the underlying causes of MS, creating cutting-edge treatment options, and enhancing the overall quality of life for those who suffer from the condition (Eva et al., 2023). Immunotherapy and disease-modifying drugs have expanded the options for managing the illness (Dargahi et al., 2017). Individuals who suspect they may have multiple sclerosis should promptly seek consultation with healthcare professionals, particularly neurologists, to get a precise diagnosis and receive suitable

therapy. Early detection and prompt intervention may significantly alleviate symptoms and slow down the progression of the disease. Examples of drugs include beta-interferon and copolymer 1, as well as immunosuppressants such as mitoxantrone and natalizumab.

2.2 Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurological disorder that primarily affects the brain, leading to the decline of memory, cognitive abilities, and behavioral patterns. It is the primary factor leading to dementia in the senior population ((Lamptey et al., 2022b). The illness is named after Dr. Alois Alzheimer, who first reported it in 1906. AD is characterized by the accumulation of abnormal protein aggregates in the brain. These comprise beta-amyloid plaques and tau tangles (Ow and Dunstan, 2014). These deposits hinders the normal passage of impulses among nerve cells, leading to cell death and the gradual deterioration of brain tissue (Breijyeh and Karaman, 2020). The symptoms include memory loss, cognitive deterioration, behavior alterations, and limitations in functionality. A thorough examination of the patient's medical history, cognitive tests, and the elimination of any potential causes that might potentially contribute to cognitive decline all help to establish the diagnosis. Advanced imaging techniques and cerebrospinal fluid (CSF) analysis may also be used in some cases. AD is often categorized into three stages: mild (early stage), moderate (middle stage), and severe (late stage). Each stage is characterized by unique symptoms and different levels of impairment (Breijyeh and Karaman, 2020). Currently, there is no known treatment for AD. However, medications such as cholinesterase inhibitors and memantine may successfully relieve symptoms and slow down cognitive decline. Supplemental therapeutic measures, such as occupational therapy and cognitive training, may also provide benefits (Hogan et al., 2008). The current research focuses on understanding AD’s underlying causes and developing effective treatment strategies. The quality of life for those who are suffering from the disorder and their caregivers may improve with increased awareness and prompt intervention. AD not only affects those who are afflicted with it, but it also places a significant burden on their caregivers. Support groups, education, and resources are essential for caregivers of individuals with AD. Individuals experiencing memory or cognitive difficulties and their caregivers should prioritize seeking medical advice for a comprehensive evaluation and appropriate intervention. Early detection may lead to more efficient readiness and intervention strategies.

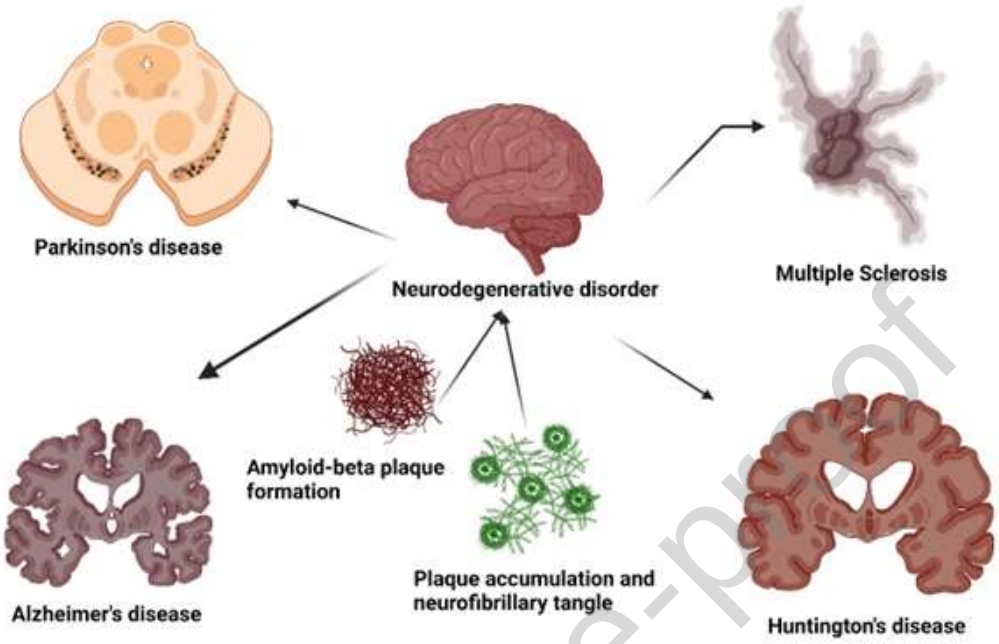


Fig. 2. Illustration of various neurodegenerative disorders such as Parkinson's disease, Multiple sclerosis, Alzheimer's disease, and Huntington's disease.

2.3 Parkinson's disease

A progressive decline in motor function is the hallmark of Parkinson's disease (PD), a neurological disorder. PD often results from the gradual deterioration of neurons that produce dopamine in the brain, particularly in a region called the substantia nigra (Hogan et al., 2008). Dopamine is a neurotransmitter involved in regulating and coordinating precise muscle movements (Gepshtein et al., 2014; Lamptey et al., 2022b). The cause of PD is not well understood; however, it is thought that genetic and environmental factors have a role. The symptoms include tremors, bradykinesia, stiffness, postural instability, and several other symptoms (Khatri et al., 2020). The diagnosis of PD mostly depends on assessing clinical symptoms and medical history due to the absence of a definitive diagnostic test. Neurological testing and, sometimes, imaging studies may be used to rule out other illnesses (JC and RA, 2018). Levodopa, a drug that acts as a dopamine replacement, is often used to alleviate motor symptoms. Furthermore, physicians may also prescribe supplementary medications, such as dopamine agonists and MAO-B inhibitors (Kulisevsky, 2022). PD progresses gradually, with the severity and variety of symptoms varying across individuals. In

the latter stages, individuals may have difficulties with verbal communication, swallowing, and cognitive functions. PD may cause several non-motor symptoms, including sleep disturbances, changes in mood, and cognitive deterioration (Mack and Marsh, 2017). Participating in consistent physical activity, especially activities that improve balance and flexibility, may be beneficial for efficiently managing symptoms and maintaining overall well-being. Physical therapy may also improve mobility. Ongoing research aims to better understand the underlying mechanisms that contribute to PD and develop more effective therapy strategies. Enhanced awareness is essential for timely recognition and response (Hughes, 1994). People who are experiencing Parkinson's disease symptoms or their caregivers should seek medical attention right away for a thorough evaluation by a neurologist. The quality of life for PD patients may significantly improve with early detection and appropriate intervention (Jankovic and Aguilar, 2008)**.**

2.4 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also referred to as Lou Gehrig's disease, is a degenerative neurological condition characterized by the gradual deterioration of nerve cells in the brain and spinal cord. ALS causes the deterioration of motor neurons, the nerve cells that govern voluntary muscle contractions (Lamptey et al., 2022b; Zarei et al., 2015). As the motor neurons deteriorate, the brain's capacity to initiate and regulate muscular action diminishes. The etiology of ALS remains poorly understood, with both genetic and environmental factors potentially contributing to its pathogenesis. Typical signs of this disorder are muscle weakness, muscle wasting, difficulties with speaking and swallowing, and breathing issues. Sporadic ALS and familial ALS are the two categories into which it may be classified (Masrori and Damme, 2020). The diagnosis of ALS mostly relies on clinical symptoms and the systematic exclusion of other illnesses since there is yet no diagnostic test accessible for this ailment. Electromyography (EMG) and nerve conduction investigations are often used to evaluate the effectiveness of muscles and motor neurons. Riluzole, an FDA-approved pharmaceutical, can decelerate the advancement of ALS by mitigating the harm inflicted upon motor neurons (Rg et al., 2012). Edaravone, an adjuvant medication authorized by the FDA, is prescribed for the treatment of ALS and can decelerate the gradual deterioration of physical abilities (Neupane et al., 2023). To optimize the well-being of people with ALS, it is imperative to effectively address symptoms and provide essential therapies such as physical and occupational therapy, breathing assistance, and communication aids. ALS generally follows a

progressive trajectory, with the pace of advancement differing across people (Hogden et al., 2017). Regrettably, there is now no remedy for the condition, and most patients with ALS die due to respiratory failure within a few years following the appearance of symptoms. Current efforts are concentrated on comprehending the fundamental processes of ALS and developing effective therapeutic solutions. Heightened consciousness is crucial for prompt identification and reaction. For those who have it and their families, ALS is a debilitating condition that causes significant difficulties. It's crucial to offer support, put together a team of specialists from various fields, and consistently conduct research to effectively manage the effects of ALS on those who have the disease (Hogden et al., 2017)

2.5 Huntington's diseases

Huntington's disease (HD) is an inherited and advancing neurological ailment that affects both the cognitive and physical aspects of an individual (Roos, 2010). The condition arises from a genetic mutation in the huntingtin gene (HTT), synthesizing a defective variant of the huntingtin protein (Hogan et al., 2008; Schulte and Littleton, 2011). This mutation leads to the deterioration of specific brain regions, resulting in a various physical, cognitive, and mental problems. HD is an autosomal dominant genetic illness, indicating that a single copy of the defective gene from either parent is sufficient for developing the disease. The mutation entails an enlargement of the CAG repeat in the HTT gene (Saudou and Humbert, 2016). There is a positive correlation between the number of CAG repeats, the age at which symptoms begin, and the severity of those symptoms. A clinical diagnosis of HD is often established by identifying distinctive symptoms and considering the patient's family history. Genetic testing, which detects the presence of the HTT gene mutation, may confirm the diagnosis (Schneider and Bird, 2016). Although HD cannot be cured, symptomatic medication and supportive care may effectively alleviate symptoms. Prescriptions may be given to reduce motor symptoms and psychological problems and enhance the general quality of life. An interdisciplinary strategy, including healthcare experts such as neurologists, psychiatrists, physical and occupational therapists, and genetic counselors, is often necessary to address the intricate requirements of people with HD. Genetic testing for HD might provide information on an individual's susceptibility to developing or passing on the condition. Individuals contemplating genetic testing are advised to get genetic counseling to comprehend the possible ramifications (McGarry et al., 2020). Continuing research endeavors to gain a deeper

comprehension of the fundamental processes of HD and create viable therapeutic approaches or remedies. Enhancing consciousness is vital for aiding impacted persons and their families and advancing research and access to services. For both those who have the disorder and their families, Huntington's disease presents significant challenges. Genetic counseling, timely diagnosis, and comprehensive treatment are crucial elements in the management of HD and in addressing its multifaceted effects on people's lives (McGarry et al., 2020).

3. Major Molecular Mechanisms Involved in NDs

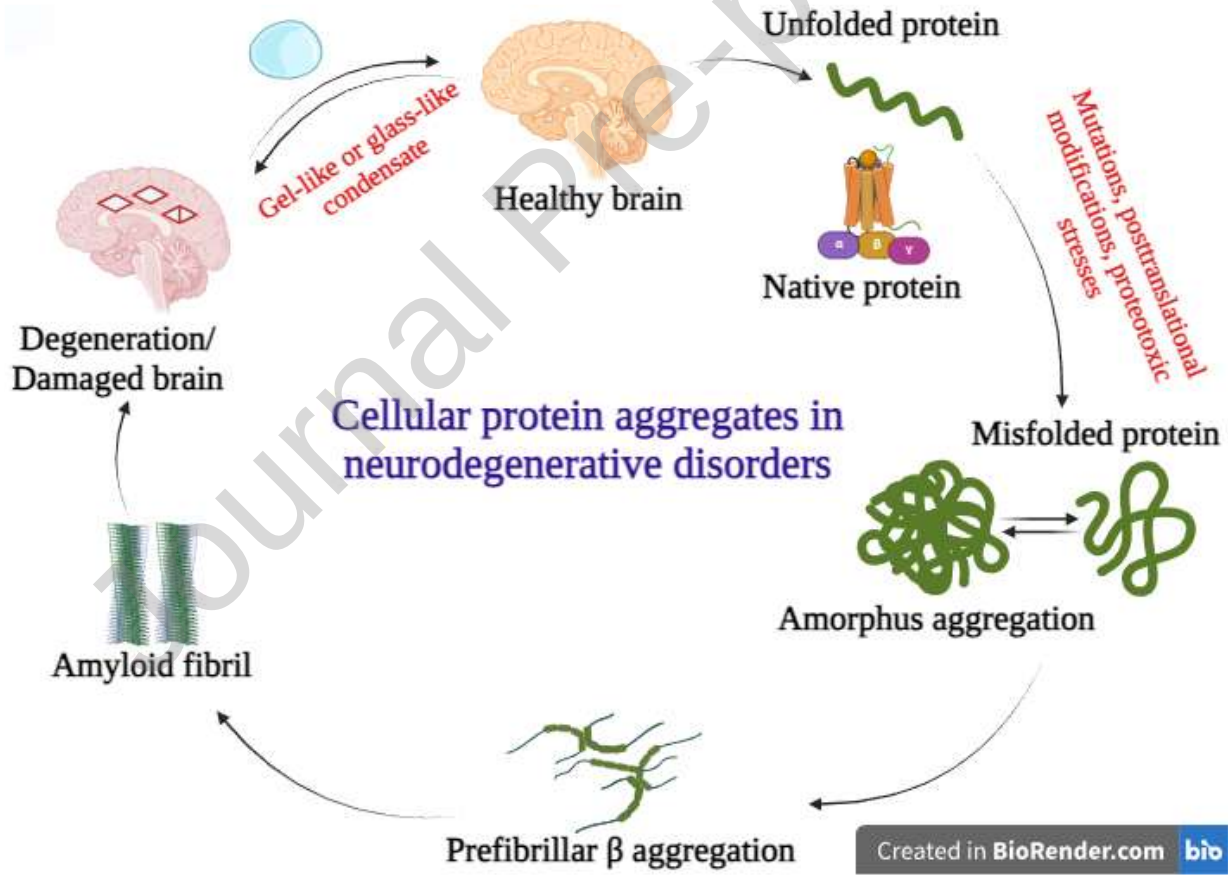
Neurodegeneration is a complicated process that happens when the functions of specific cells (nerve cells) in the brain subside; it is often connected to aging (Wareham et al., 2022). In neurodegeneration, some proteins in the brain do not function correctly, and this causes clumps to form in different parts of the brain (Jellinger, 2010). Other issues caused by neurodegeneration such as is inflammation, energy deficiency, and DNA damage. These gradually increase their intensity resulting in cell death (McEwen, 2017). There are different ways that the cells can die, such as such as turning off or breaking apart. In the next part, primary molecular mechanisms regarding neurodegeneration have been discussed in detail; **Fig. 3A** represents crucial mechanisms behind NDs**.**

3.1. Abnormal Protein Aggregation and Misfolding

Misfolded proteins that build up and clump together are common signs of various brain diseases. They are thought to be the primary reason for these disorders (Ashraf et al., 2014; Khanam et al., 2016). Aggregation occurs when a misfolding protein sticks together because of specific interactions with other protein parts (Ajmal, 2023). It often starts with a small particle or seed that starts the process. This process can then move to other proteins and change them into harmful forms (**Fig. 3A**). Usually, misshapen proteins create clumps of beta (β)-sheet structures when small groupings of proteins start to come together (Ashraf et al., 2014). Proteins clump together to make extracellular or intracellular inclusions. NDs have different kinds of protein clumps in them (**Fig. 3A**). For instance, in AD, there are β-amyloid (Aβ) plaques and misfolded Tau proteins **(Fig. 3B)** (Gulisano et al., 2018). In PD and HD, there are also misfolded Tau proteins. PD and other disorders have α-synuclein pathological inclusions. However, in ALS and frontotemporal dementia, there is TAR DNA-binding protein 43 (TDP-43) **(Fig. 3B)** (Brettschneider et al., 2015; Gao et al., 2018; Jo et al., 2020). Amyloid fibrils are big, are insoluble,

and can join to form amyloid plaques. Amyloid oligomers are smaller, soluble in water, and spread across the brain **(Fig. 3B)**. The build-up of Aβ has a significant impact, such as making reactive oxygen species (ROS), reactive nitrogen species (RNS) and causing inflammation that leads to a dangerous cycle (Tönnies and Trushina, 2017). This can cause problems with mitochondria thinking skills, eventually leading to brain degeneration. In preventing protein clumping, brain cells have a system of complicated processes to keep the right balance of proteins. Molecular chaperones help proteins fold correctly and eliminate the bad ones so they don't cause harm (Swerdlow, 2020). Because these cell systems are essential for keeping cells healthy, it would be helpful to learn how they are controlled in neurodegeneration. This information could explore unique ways to treat NDs.

(A)



(B)

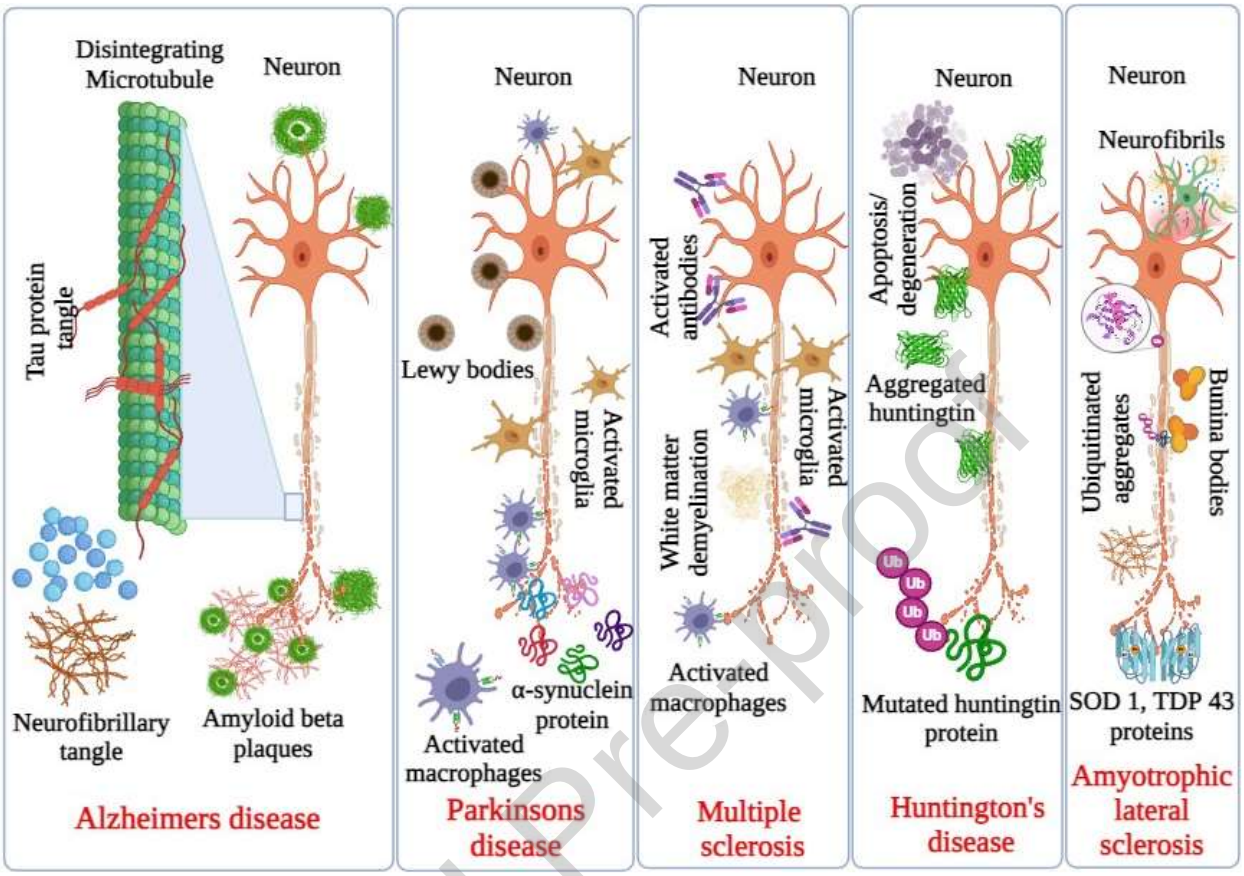


Fig. 3: Schematics show the steps involved in cellular protein aggregation associated with neurodegeneration: **(A)** represents the native structure of protein transformed in misfolding due to stresses, which impact amyloid protein fibrils and initiation of neurodegeneration. **(B)** Different proteins and their aggregates are involved in AD, PD, MS, HD, and ALS.

3.2. Oxidative Stress in NDs

Globally, now it is recognized that oxidative stress causes changes in the biochemical and biomolecular parts of the body, leading to diseases such as AD, MS, ALS, HD, and PD (Olufunmilayo et al., 2023; Sayre et al., 2008; Singh et al., 2019). However, it's important to note that small amounts of ROS and RNS are essential for signaling in the brain. They help with communication between cells and memory. However, too many of these reactive species can harm parts of cells, such as DNA, proteins, and fats (Di Meo et al., 2016; Hancock et al., 2001; Juan et al., 2021). This can cause stress and lead to nerve cells dying. Oxidative stress happens when antioxidants don't work well or there are too many ROS/RNS (**Fig. 4**). So, having the right mix of oxidants and antioxidants is essential to keep nerve cells working well. Also, as mentioned before,

the human brain is easily damaged by oxidative stress because it uses a lot of oxygen, has a lot of fatty acids and metals, and has low levels of glutathione (Jelinek et al., 2021; Salim, 2017). Mitochondria mainly make intracellular ROS (Collin, 2019). When oxygen molecules are broken down, they produce a superoxide anion called O^{2-} Starting from O^{2-}, various harmful molecules are made, such as hydrogen peroxide, hydroxyl radical, hypochlorous acid, and hydroperoxyl radical (Turrens, 2003). In mitochondria, manganese superoxide dismutase removes a toxic substance called superoxide. This creates hydrogen peroxide, which can become a harmful molecule called hydroxyl radical in the Fenton reaction process (Indo et al., 2015). The presence of iron and copper speeds up this process. The hydroxyl radical can also be made in the Haber-Weiss reaction (Kehrer, 2000). A reaction begins with superoxide anion and hydrogen peroxide. Inside cells, reactive oxygen species (ROS) can be created in peroxisomes when they break down molecules for energy. The body makes hydrogen peroxide as a result of ROS (Collin, 2019; Fransen et al., 2012). In normal conditions, the enzyme catalase helps to control the amount of hydrogen peroxide. NADPH oxidase (NOX) is an enzyme that makes ROS. Superoxide and hydrogen peroxide are the main ROS. NOX enzymes are found in the body's microglia, neurons, and astrocytes (Nayernia et al., 2014). The neurovascular system is a network of nerves and blood vessels (Tarafdar and Pula, 2018). Around the world, there is strong evidence that NOX enzymes are involved in different brain diseases such as AD, PD, and HD. Illnesses such as PD and AD can give the body more xanthine oxidase, which can cause more damage from oxidants (Ma et al., 2017). Such as ROS, RNS can cause changes in DNA, proteins, and lipids through nitrosylation reactions. In people with AD, their brains show signs of damage caused by harmful substances called ROS (**Fig. 4**). This damage can be seen in proteins, DNA, RNA, and fats in the brain (Tönnies and Trushina, 2017). In PD, higher levels of markers show the body is under a lot of physical and chemical strain. These markers include 8-hydroxy-2-deoxyguanosine, 4-hydroxy-2-nonenal (which shows fat is being damaged), protein carbonyls, and 3-nitro-tyrosine (proteins are being damaged) (Hustad and Aasly, 2020). This causes harmful effects on the brain and its functions, which are further converted into NDs.

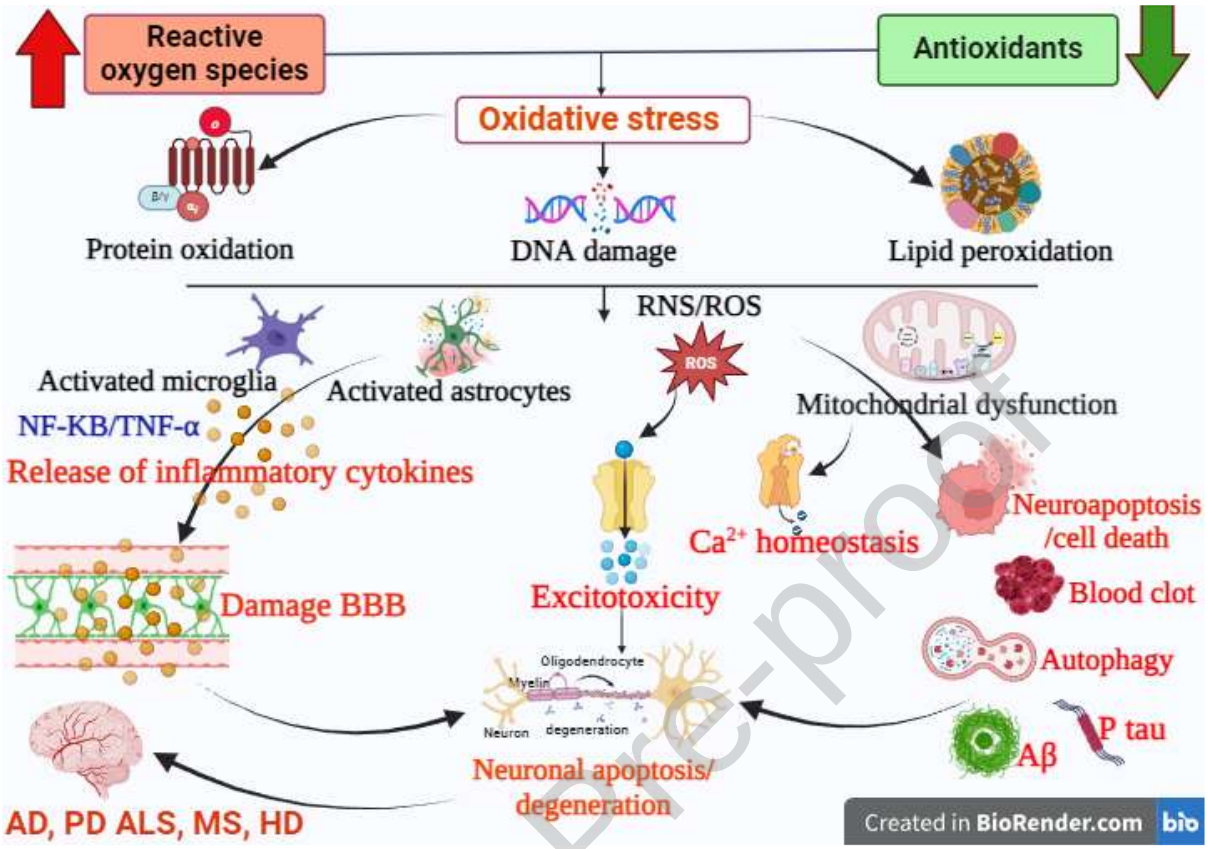


Fig. 4: Diagram illustrating the imbalance in antioxidants, RNS/ROS, or oxidative stress level influences NDs, which damages cellular macromolecules such as lipids, DNA, and proteins. Activated astrocytes and microglia release inflammatory cytokines and chemokines in response to mitochondrial malfunction, accelerating tissue death/cellular apoptosis, excitotoxicity, Ca^{2+} homeostasis, and autophagy, which further cause neurodegeneration.

3.3. Neuroinflammation and Microglial Activation

Inflammation is the body's defense mechanism against infections, injuries, toxins, and other types of damage (Ransohoff et al., 2015). Neuroinflammation is when the central nervous system gets inflamed. It involves different types of cells working together (Kwon and Koh, 2020). These cells work together because of certain chemicals in the brain. Microglia and astrocytes are the primary cells that cause inflammation in the brain (**Fig. 5**) (Gadhave et al., 2024). Usually, microglia cells help keep the brain healthy and do different jobs to fix nerve cells, such as getting rid of waste, organizing connections between nerve cells, reacting to harmful substances, and cleaning up abnormal proteins (Ransohoff et al., 2015). For instance, in the early stage of AD,

special cells in the brain can help protect it from damage by cleaning out a harmful protein called Aβ (Edler et al., 2021). Active microglia help astrocytes grow, which protects and repairs damaged brain cells. When the brain is injured, special brain cells called astrocytes become activated and change in size and chemical makeup. They also start making more protein fibers and multiplying and moving more (Fatoba et al., 2020; Vainchtein and Molofsky, 2020). Although neuroinflammation helps protect the brain, too much of it can harm the brain. Getting older, having specific health problems, and getting sick from viruses can cause long-lasting swelling in the brain, leading to brain damage over time. Neuroinflammation happens when the Nuclear Factor Kappa B (NF-κB) gets activated (Ahmad et al., 2022; Ransohoff et al., 2015). This protein helps control the activity of various genes that are part of inflammation, cell death, cell survival, and the development of nerve cells (**Fig. 5**). When NF-κB is activated, microglia produce more inflammation-causing genes and substances such as iNOS, COX-2, TNF-α, IL-6, IL-1, and ROS (Goldmann et al., 2013). This helps us understand how these cells react in different brain disorders. In summary, inflammation in the brain is the leading cause of many neurodegenerative diseases such as MS, PD, AD, HD, and ALS (Triantafyllakou et al., 2022). That's why it's crucial to find ways to stop neurodegeneration by targeting this inflammation.

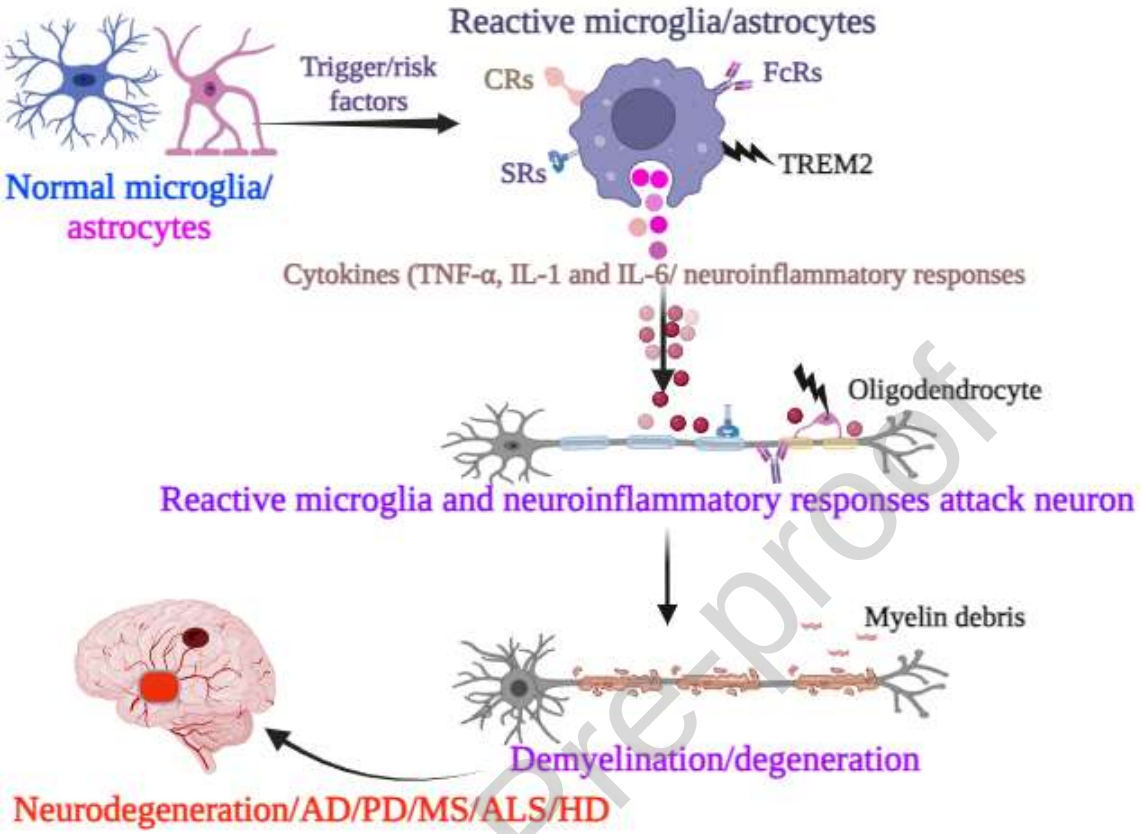


Fig. 5: Reactive immune cells and inflammatory responses involved in demyelination /neurodegeneration in NDs.

3.4. Mitochondrial Dysfunctions in NDs

The brain is involved in crucial body functions; therefore, it requires a lot of energy and can only be obtained from oxygen. The brain needs a lot of oxygen, about 20% of the body's total supply. One of the things in the brain called Na^+ K^+ ATPase uses a lot of energy to help the brain cells work correctly (Watts et al., 2018). The brain uses a lot of energy for its activities. It mainly gets this energy from oxidative phosphorylation, which produces an ATP molecule. The brain cells use about 4.7 billion ATP molecules every second (Zhu et al., 2018, 2012). In addition to providing energy, mitochondria also do other essential things in the brain, such as controlling how messages are sent between brain cells and ensuring cells grow and die correctly (Casanova et al., 2023; Shen et al., 2022). Because these functions are necessary to keep the mitochondria working well, mitochondria stay healthy because of different processes such as making new ones, splitting apart, joining together, and getting rid of damaged ones before they can harm the whole cell (Tönnies and Trushina, 2017). Because neurons cannot regenerate quickly, problems with mitochondria can

cause injury to the neurons and brain cells. Mitochondria produce massive amounts of ROS because many electrons are utilized in body functioning (**Fig. 4**). ROS also directly damages the components of mitochondria, leading to a harmful cycle (Tirichen et al., 2021; Zorov et al., 2014). Exposure to ROS can stop the iron-sulfur centers in the electron transport chain. Long-term exposure can also harm lipids, proteins, and DNA. ROS easily damages the inner part of the mitochondria because it's close to where the ROS are made (Juan et al., 2021; Singh et al., 2019). ROS can cause damage to cell membranes, which affects essential processes in the cell and stops energy production in the mitochondria. Recent research has found that broken parts of cells called mitochondria might cause inflammation by starting a harmful signaling process (Napolitano et al., 2021; Singh et al., 2019). Due to different sources of stress, mitochondrial DNA can be moved outside cells by making tiny bubbles (**Fig. 4**). After they are released, these cysts can cause an immune response by attaching to receptors that sense danger and can act as damage signals. Many studies have found that problems with a part of the cell called the mitochondria happen early in brain diseases (Aarts et al., 2017; Missiroli et al., 2020). In short, the brain requires a lot of energy to work, and the mitochondria are crucial. Hence, mitochondrial dysfunction can cause severe problems and lead to neurodegeneration.

4.1 Blood-Brain barrier (BBB)

The cerebrovascular system has a semipermeable junction called the blood-brain barrier (BBB) – figure 6, which possesses vital characteristics that govern CNS homeostasis. A restricted amount of transcellular transport does occur. Still, the adult blood–brain barrier (BBB) is made up of capillary endothelial cells (ECs) joined tightly by adherens junctions (AJs) and tight junctions (TJs). These structures inhibit paracellular transit and have poor pinocytotic activity. Furthermore, pericytes, microglia, and closely related perivascular astrocytic end feet impact the BBB. These various cell types play crucial roles in BBB induction and preservation by controlling brain endothelial cell migration, proliferation, and vascular branching (Attwell et al., 2010).

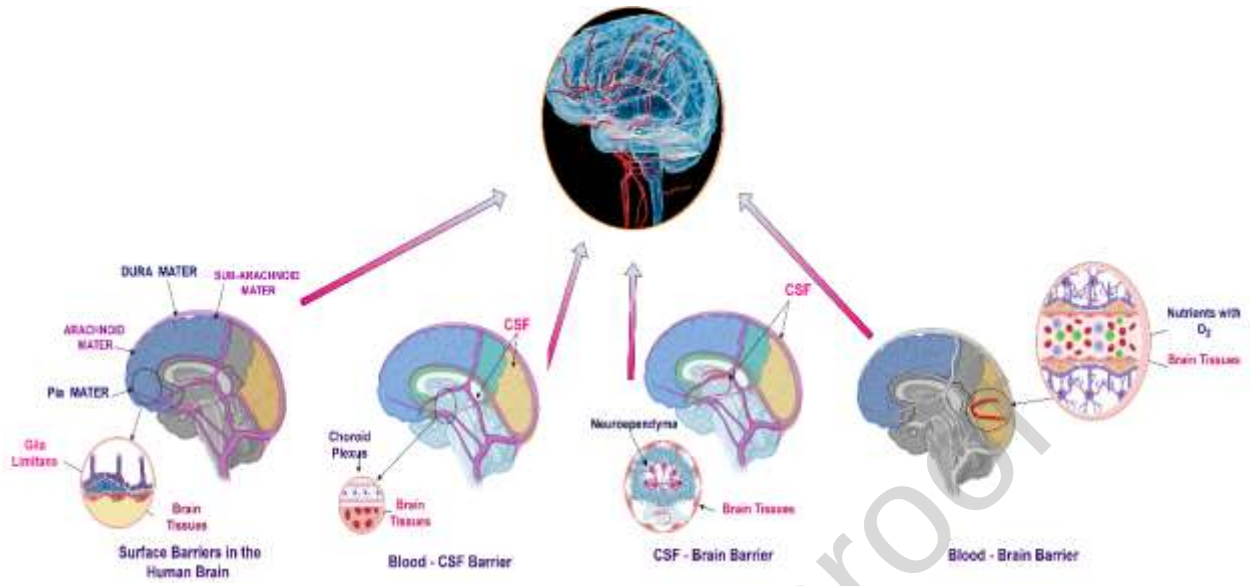


Fig. 6: Schematic representation of brain barrier and its types

About 20% of the BBB's surface, or abluminalis covered in pericytes, which have been inserted in the vascular cell membrane. These cells can control the blood circulation in brain capillaries by contracting and relaxing because they have contractile proteins (**Fig. 7).** The basement membrane forms the inner and outer covering, formed by the extracellular matrix and pericyte. By creating a complex network around BCECs, astrocyte end-feet encapsulate the brain endothelial capillary nearly entirely, preserving the structural integrity of the blood-brain barrier and boosting tight junctions. It also facilitates intercellular interaction among neurons and BCEC to control blood flow and arterial contraction/dilution by neuronal responses. Furthermore, astrocytes are thought to be the major workhorse of the central nervous system (CNS) due to their multifaceted activities in preserving brain homeostasis, cleaning synapses, and protecting against injuries. Microglia are important for safeguarding CNS homeostasis and mediating immunological control in the brain (Persidsky et al., 2006; Saenz del Burgo et al., 2014). Researchers continue to be interested in exosomes because of their biocompatibility and bilayer lipid structure, which shields the cargo within and allows exosomes to cross nearly all barriers, particularly the blood-brain barrier (Chavda et al., 2023).

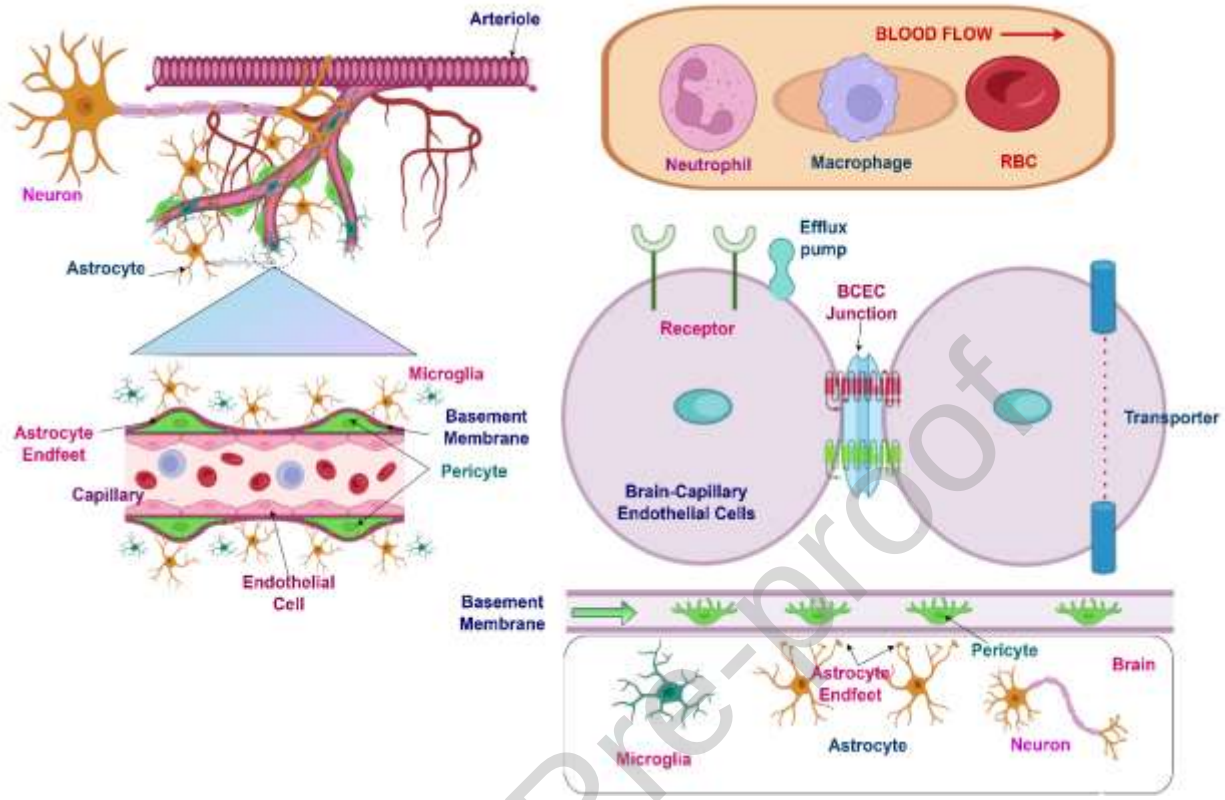


Fig. 7: Diagrammatic illustration of the neurovascular sections, which are made up of vascular cells (endothelial cells, astrocytes) and neurons. BCEC: Brain capillary endothelial cells

4.2 Blood-Cerebrospinal Fluid Barrier (B-CSF)

While many neurologic illnesses have focused on the breakdown of the blood-brain barrier, the concept of the breakdown of the blood-CSF barrier is relatively new. An increasing amount of research indicates that the B-CSF barrier is important for the transmission of inflammatory responses from the peripheral to the central nervous system and plays a part in the development and progression of several neurological illnesses (Erdő et al., 2018). The choroid plexus (CP), found in the lateral, 3rd, and 4th ventricles, comprises one layer of ciliated epithelium, packed with fluid connective tissue, and fenestrated blood arteries. The CP produces and secretes CSF. High permeability made possible by the fenestrated arteries allows CP epithelium cells to generate CSF from blood. An osmotic differential that pulls in water is created at the B-CSF by the constant influx of Na^+, Cl^-, and bicarbonate ions entering the ventricular system via ion channels and co-transporters.

The most prevalent neurological illness, Alzheimer's disease (AD), is characterized by cognitive decline, synapse loss, and dementia. The primary cause of Alzheimer's disease (AD) is an excess of β-amyloid that leads to the build-up of beta-amyloid clumps in brain tissue. Beta-amyloid removal from brain tissue is aided by the CP and B-CSF obstruction. Megalin, a multi-ligand endocytic receptor, has been demonstrated to have a role in β-amyloid elimination by moving β-amyloid from CSF across the B-CSF barrier (Spuch et al., 2015).

T- and B-lymphocytes, as well as macrophages, are increased in Multiple sclerosis (MS) patients' white matter, which is characterized by numerous inflammatory lesions. The brain's protective barriers allow inflammatory cells to enter the central nervous system. Particularly, lymphocyte entrance into the CSF and subsequent upregulation of particular IgG antibody production occurs at the CP. It has been demonstrated that T-cells, particularly CD4+ T-cells, control immune cell transportation via the B-CSF barrier by producing IFN-γ. Following local IFN-γ signaling, adhesion molecules such as VCAM-1 and ICAM-1 are upregulated (Kivisäkk et al., 2003; Kunis et al., 2013).

4.3 Blood-Tumor Barrier (BTB)

The blood–tumor barrier (BTB) is created when the blood–brain barrier is compromised during the growth of a tumor. Despite the BTB's greater permeability than the BBB, inadequate medication accumulation in brain tumors results from its uneven perfusion and permeability to small and big molecules (Arvanitis et al., 2020). Abnormal distribution of pericytes, loss of astrocytic end feet, and disruption of neural connections are the hallmarks of BTB. Additionally, the integrity of the BBB can be disrupted. In brain tumors that are primary or metastatic, the BTB limits the effectiveness of chemotherapy and promotes tumor growth (Blethen et al., 2021).

Some medications may not be able to enter the brain tumor microenvironment when the BTB structure is present. Irregular permeability is another feature of BTB that uniformly restricts medication diffusion and penetration within tumors. To increase the delivery efficiency, it is crucial to increase the permeability of BTB. The physical distinction between a primary CNS tumor and the BTB in brain metastases of breast cancer may aid in the molecular explanation of permeability variations and variability. In mice with brain metastases from breast cancer tumors, (Imran et al., 2023) the density of blood vessels is 40–80% lower than that of the healthy brain (Yano et al., 2000).

5. Advanced/novel therapies to treat NDs.

5.1. Gene therapy

The application of gene therapy for effectively treating neurodegenerative disorders has garnered significant attention as a promising approach based on modifying genetic deficits and delivering therapeutically active proteins (Gowing et al., 2017). This avenue holds the potential for treating conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) (Chen et al., 2020). Gene therapy involves introducing new genes directly into patients with neurodegenerative disorders using carriers such as plasmid DNA or viral vectors (Savić and Schwank, 2016). Another approach includes modifying genes *in vitro* and transplanting these modified cells into the respective patient (Naldini, 2011). The altered gene plays a crucial role in restoring missing gene functions within cells, contributing to treating of various neurodegenerative disorders (Ling et al., 2023). The process can be divided into three main steps: identifying the target gene, selecting an appropriate vector, and determining the suitable transfer mode (Naldini, 2011). Viral vectors, specifically Adeno-associated viruses (AAVs) and lentiviral vectors (LVs), have been recognized as effective choices for gene therapy in neurodegenerative diseases (Piguet et al., 2017). There are two types of gene therapy: *in vivo* gene therapy and *ex vivo* gene therapy (Canver, 2009). Recombinant viral vectors are employed in the *in vivo* delivery of therapeutic genes. This method, often the first and most widely adopted approach, involves local delivery in specific brain regions, such as parenchymal brain regions, through stereotactic injections, and has been successfully utilized for lysosomal storage diseases, Huntington's disease, and PD (Piguet et al., 2017). Notably, Adeno-associated virus (AAV) vector-based *in vivo* gene therapy has recently been discussed as an effective treatment for neurodegenerative disorders. The second category of gene therapy is known as *ex vivo* gene therapy. In essence, this method involves genetically modifying cells outside the body, leading to the generation of crucial therapeutic factors. The designed genetic modifications must be transplanted into patients for effective disease treatment. In ND, *ex vivo* gene therapy specifically entails modifying hematopoietic stem cells, purified from either blood or bone marrow, using Lentiviral Vectors (LVs). Subsequently, the transduced cells undergo autologous transplantation. This process results in the renewal of the microglia compartment, expressing transgenic therapeutically active proteins after hematopoietic reconstitution. In conclusion, *ex vivo* gene therapy effectively delivers therapeutically activated

proteins to the targeted brain site (Piguet et al., 2017). Gene therapy offers a more cost-effective alternative, demonstrating its humane aspects. Additionally, gene therapy addresses the limitations associated with the blood-brain barrier in traditional treatments (Puranik et al., 2021). To realize the promising outcomes of gene therapy, careful consideration must be given to the safety and efficacy of this treatment in patients with neurodegenerative disorders (Ling et al., 2023). Despite considerable advancements, clinical trials have fallen short of achieving satisfactory therapeutic effects through gene therapy. Hence, there is a pressing need to focus on novel therapeutic targets, identify new vectors, and establish reliable delivery routes for transgenes. These efforts aim to enhance the effectiveness of gene therapy in the context of neurodegenerative disorders (Chen et al., 2020).

5.2. Immunotherapy

To address neurodegenerative disorders (NDs), current therapeutic approaches primarily focus on symptomatic treatments, unfortunately lacking a direct impact on the root cause of these disorders. Consequently, there is an imperative for advanced therapies capable of either curing or controlling disease progression. Recent findings underscore the pivotal role of immunotherapy in both managing and impeding the advancement of NDs. Specifically, the immune system, or its components, exhibits promising potential to combat aggregated proteins and misfolded substances implicated in NDs. In the context of immunotherapy development, using antibodies and specific antigens to elicit an adaptive immune response against NDs is currently in progress (Mortada et al., 2021). For instance, antibodies targeting alpha-synuclein aggregation and propagation blockers are being investigated. The potential mechanism underlying immunotherapy in ND involves the inhibition of extracellular alpha-synuclein in the brain, subsequently diminishing the pathological burden and exerting control over disease progression (Shin et al., 2020). Earlier immunotherapeutic endeavors concentrated on specific targeting and clearance of extracellular protein aggregation, such as in Alzheimer's disease involving beta-amyloid. In contrast, contemporary immunotherapy for NDs emphasizes intracellular proteins, characterized by their toxic nature and significance as hallmarks of NDs (Valera and Masliah, 2013). The modulation of immune cells in NDs is considered as critical, although the impact of either boosting or suppressing the immune system on neurodegeneration remains uncertain (Valera and Masliah, 2013). Early-stage human trials related to active amyloid beta vaccination were prematurely halted due to safety

concerns (Brody and Holtzman, 2008). In Alzheimer's disease, antibodies targeting beta-amyloid serve as an immunotherapeutic strategy to mitigate brain deposition of beta-amyloid. Notably, aducanumab, a human monoclonal antibody recognized as the first disease-modifying treatment, has received approval from the US FDA for addressing beta-amyloid aggregation (Hoque et al., 2023). One major obstacle in immunotherapy is the blood-brain barrier (BBB), a critical impediment to the effective delivery of drugs and compounds to the brain. Overcoming this challenge involves the utilization of nanocarriers with surface modifications, a strategy that assumes significance in the management of NDs (Hoque et al., 2023). The targeting of inflammatory mediators, such as TNF-α, interleukins, granulocyte-macrophage colony-stimulating factor, pyrin domain–containing 3, peroxisome proliferator-activated receptor gamma (PPAR-γ), and glucagon-such as peptide 1 (GLP-1), has been reported as immunotherapy for neurodegenerative diseases (NDs). Additionally, vaccine therapy has been explored, employing both active and passive immunization with suitable types of antibody fusion (monoclonal) or specific proteins/antigens inducing adaptive immunity. However, the use of antibodies in treating NDs faces several limitations, including high cost, adverse side effects, and the requirement for frequent administration (Mortada et al., 2021). Recent clinical trials on prasinezumab monoclonal antibody (phase II) have demonstrated its application in targeting and reducing free serum alpha-synuclein (Jankovic et al., 2018). Another immunotherapy utilizing BIIB054, an N-terminus targeting monoclonal antibody, has shown safe application in targeting alpha-synuclein in serum (Weihofen et al., 2019). Despite significant developments, there is a need to focus on investigating the types of immunogenic particles, the route or mode of delivery, and their mechanisms of action.

5.3. Therapies involving advanced drug delivery system

Due to the high prevalence of neurodegenerative diseases and the limited efficacy of symptomatic treatments, there is a growing interest in exploring advanced materials that deliver drugs effectively for the management of these life-threatening conditions. Biomaterials have emerged as promising candidates for various applications, encompassing regenerative medicine and understanding disease pathogenesis (Bordoni et al., 2020a). Previously, biomaterials were referred as “non-vital materials used in medical devices, intended to interact with biological systems.” Currently, biomaterial are defined as a material that interacts with living tissues and executes specific functions without adverse effects (Masaeli et al., 2019; Pantwalawalkar et al., 2022). Key

characteristics of biomaterials encompass biocompatibility, biodegradability, and bio-inert nature. (Bordoni et al., 2020a; Imran et al., 2023; Wang et al., 2004). To date, a diverse array of biomaterials, such as hydrogels, nanoparticles, nanoemulsion, self-assembling peptides, nanofibers, and carbon-based nanomaterials, has been investigated for their potential applications in neurodegenerative diseases (Bordoni et al., 2020a) (Imran et al., 2023). The choice of a biomaterial is contingent upon various physical, chemical, mechanical, and biological properties, including wettability, softness, roughness, chemical composition, functional groups, corrosion properties, yield, tensile strength, ductility, fatigue, etc (Stratakis, 2018). Recently, a notable preference for nano-biomaterials has been characterized by nanostructures ranging from 1 to 100 nanometers (Imran et al., 2023). This strategic design aims to surmount the challenges associated with the BBB in treating neurodegenerative disorders (Bordoni et al., 2020b). In brief, inorganic nanoparticles and their composites, such as cerium oxide nanoparticles, manganese tetraoxide nanoparticles, yttrium oxide, iron oxide, and copper nanoparticles, have been explored as biomaterials against oxidative stress in neurodegenerative diseases. These inorganic nanomaterials play crucial roles in neurodegenerative diseases, functioning as antioxidants, inducing dopamine production, improving redox activity, and serving as enzyme mimetics (Eleftheriadou et al., 2020). Furthermore, using metal nanoparticles, such as gold and silver, contributes to infection treatment based on their potential for cell proliferation, tissue recovery, antioxidant activity, and antimicrobial potential. Quantum dots are crucial in imaging and diagnosing neurodegenerative diseases due to their unique and versatile characteristics. Lipidic nanocarriers provide a platform for encapsulating cargo molecules, enabling the delivery of various molecules using bilayer lipidic nanocarriers (Kumar et al., 2021). PEGylated-lipid nanoparticles coupled to an anti-Fas ligand antibody were found after therapeutic targeting in an ischemia area of the brain, as shown by Lu et al. In this work, coupled lipid nanoparticles containing 3-n-butylphthalide, a component of celery oil, were effectively transported to the ipsilateral region of an ischemic brain in male C57BL/6J wild-type mice. (Shabani et al., 2023). In summary, biomaterials in neurodegenerative diseases offer several advantages, including controlled and targeted drug release, cost-effectiveness, scalability, stimuli-responsive nature, targeted route administration, and customization for personalized medicine. Despite these advancements, overcoming limitations such as the BBB, assessing toxicity through immunotoxicity and cytotoxicity, and addressing

immunological concerns, including body clearance and adverse immune reactions, remains a critical challenge.

6. Clinical relevance of novel ND therapies

The clinical investigation of specifically designed novel therapies is essential to substantiate their effectiveness and therapeutic success (Kumar et al., 2022). Given the intricate nature of neurodegenerative diseases (NDs), the development of disease-modifying treatments instills fresh optimism in the biomedical field to effectively manage NDs (Katsuno et al., 2012). According to the literature, advanced therapies for NDs offer numerous advantages, including cost-effectiveness and high-quality treatment (Kumar et al., 2022). However, despite these advancements, concerns persist regarding the safety and efficacy of these sophisticated therapies. Many candidate molecules exhibit limited or no disease-modifying capabilities *in vivo* applications (Katsuno et al., 2012). Disappointingly, clinical trials of molecularly targeted therapy in NDs have yielded suboptimal results, with a critical issue being the insufficient understanding of the molecular pathogenesis of ND. Apoptotic cell deaths have been identified in human specimens, adding to the complexity, and the mechanism of neuron death remains unclear with advanced molecular therapies in NDs (Katsuno et al., 2012). The assessment of the efficacy of advanced therapies in pre-clinical trials poses a significant challenge in treating NDs (Katsuno et al., 2012). Furthermore, even after conducting preclinical studies, analyzing extensive data on therapies employed in these studies for NDs becomes a major hurdle in confirming the selection of precise candidates for subsequent clinical studies (Kumar et al., 2022).

Consequently, this review section comprehensively outlines various advanced technologies progressing through different phases of clinical trials to manage NDs. Trial code NCT05040217, Twelve people are enrolled in this open-label Phase I clinical trial of AAV2-BDNF gene therapy to treat mild cognitive impairment (MCI) and early Alzheimer's disease (AD). A growth factor for the central nervous system, BDNF controls how neurons operate in the brain's two main memory circuits, the entorhinal cortex and the hippocampus. In animal studies, BDNF decreases cell loss, promotes cell function, and creates new synapses (connections) between brain

cells. Since BDNF, the potential therapeutic protein, cannot pass through the blood-brain barrier, genetic treatment approaches will be used in this clinical study. Trial code NCT04167540, A naturally occurring protein in the brain, glial cell-line derived neurotrophic factor, or GDNF as it is more well known is a neurotrophic factor that supports and nurtures brain cells. According to research conducted in laboratories, GDNF may have neuroprotective attributes and aid in the regeneration or recovery of Parkinson's disease-affected brain cells. There doesn't appear to be a treatment available right now that can achieve this. This latest experiment uses a form of gene therapy in which non-functional genes are replaced with new ones that carry the instructions to produce a working protein at high enough concentrations to be used as a possible treatment.

Trial code NCT00663026, Patients receiving bapineuzumab showed a larger decrease in amyloid on positron-emission tomographic amyloid examination with Pittsburgh compound B (PIB-PET) and a reduction in cerebrospinal fluid phosphorylated tau (phospho-tau), which suggests target engagement and attenuated neurodegeneration, in phase 2 clinical studies involving patients with mild-to-moderate Alzheimer's disease. Individuals receiving a placebo did not show these same reductions. Trial code NCT05541627, A single intracerebral bilateral injection of AB-1001 into the striatum (caudate and putamen) will be administered to participants with early apparent HD as part of this Phase I/II, first-in-human, open-label trial to assess safety, tolerability, and preliminary effectiveness signals. Dose-limiting toxicities (DLTs), Treatment-Emergent Adverse Events (TEAEs), and Serious Adverse Events (SAEs) are the primary outcome incidences. Secondary result MRI measurements of the volumetric and anatomical components of the HD-affected brain areas. **Table 1** summarizes various novel therapies currently undergoing clinical trials for treating NDs. It confirms that most advanced therapies are in the initial phases of clinical trials, including phases 1, 2, and 3. In conclusion, the transition of advanced therapies involved in NDs is a critical step for the effective management of these disorders.

Table 1: Summarizes various novel therapies currently undergoing clinical trials for treating NDs. It confirms that most advanced therapies are in the initial phases of clinical trials, including phases 1, 2, and 3

Sr. No.	Disorders	Trial code	Delivery Route	Therapy	Phase
1.	Alzheimer's Disease, Mild Cognitive Impairment	NCT05040217	Stereotaxically administration	A Clinical Trial of AAV2-BDNF Gene Therapy in Early Alzheimer's Disease and Mild Cognitive Impairment	Phase 1
2.	Huntington's Disease	NCT05541627	Bilateral injection	A Study to Evaluate AB-1001 Striatal Administration in Adults With Early Manifest Huntington's Disease	Phase 2
3.	Parkinson Disease	NCT01564992	---	Drug Interaction With Genes in Parkinson's Disease (DIGPD)	---
4.	Sanfilippo Type A Syndrome	NCT01474343	Intracerebral administration	Intracerebral Gene Therapy for Sanfilippo Type A Syndrome	Phase 2
5.	Human Prion diseases	NCT02837705	---	Therapeutic Antibodies Against Prion Diseases From PRNP Mutation Carriers (PRNP)	---
6.	Parkinson Disease	NCT04167540	Bilateral image-guided infusion	GDNF Gene Therapy for Parkinson's Disease	Phase 1

7.	Alzheimer's Disease	NCT03634007	Intrathecal administration	Gene Therapy for APOE4 Homozygote of Alzheimer's Disease	Phase 2
8.	Alzheimer's Disease	NCT00017940	---	Gene Therapy (Human Nerve Growth Factor) for Alzheimer's Disease Clinical Trial	Phase 1
9.	Alzheimer's Disease	NCT05400330	---	Long-Term Follow-up of Gene Therapy for APOE4 Homozygote Alzheimer's Disease (LEADLTFU)	Phase 1
10.	Alzheimer's Disease	NCT00663026	Subcutaneous injection	Study Evaluating Bapineuzumab In Alzheimer's Disease Subjects	Phase 2
11.	Alzheimer's Disease	NCT00676143	IV infusion	Study Evaluating the Safety and Efficacy of Bapineuzumab in Alzheimer's Disease Patients	Phase 3
12.	Alzheimer's Disease	NCT00667810	IV infusion	Study Evaluating The Efficacy And Safety Of Bapineuzumab In Alzheimer's Disease Patients	Phase 3
13.	Alzheimer's Disease	NCT00998764	Infusion	A Long-Term Safety And Tolerability Extension Study Of Bapineuzumab In Alzheimer's Disease Patients	Phase 3
14.	Alzheimer's Disease	NCT05821153	Subcutaneous injection	Low Dose IL2 Immunotherapy in AD	Phase 1
15.	Alzheimer's Disease	NCT00112073	IV	AAB-001 in Patients With Mild to Moderate Alzheimer's Disease	Phase 2

16.	Alzheimer's Disease	NCT05792163	Oral administration	A First Time in Human Study of SNP318 as a Treatment for Neurodegenerative Diseases Including Alzheimer's Disease	Phase 1
17.	Alzheimer's Disease	NCT01229332	Continuous administration	A Safety, Tolerability, and Pharmacokinetic Study of ND0611 on the Top of Different Oral Dosage Forms of Levodopa/Carbidopa in Parkinson's Disease Patients	Phase 2
18.	Alzheimer's and Parkinson's Disease	NCT04524351	Oral administration	Posiphen® Dose-Finding, Biomarker Study in Early Alzheimer's and Parkinson's Patients	Phase 2

"The formulations related to Clinical Trials on Neurological Disorders (NDs) were gathered exclusively from the Clinical Trials website, as this data was not referenced in any existing review or research article. Below the table, it is needed to state that:

'Information collected from the web: clinicaltrials.gov on January 30, 2024'

Table 2: FDA approved drug's for the treatment of ND's

Sr. no	**Disorders**	Drug's	Reference
1	Alzheimer's Disease	Donepezil, rivastigmine, galantamine, Memantine	(Durães et al., 2018)
2	Parkinson's Disease	Levodopa, carbidopa, benserazide, tolcapone, entacapone, selegiline, rasagiline, amantadine	
3	Huntington's Disease	Tetrabenazine	

7. Future remarks

Despite advancements in biomedical science, molecular biology, genetics, and pharmaceutical sciences, there are still considerable challenges with neurodegeneration research and identifying promising therapeutics. To understand the disease pathophysiology, a clinically-relevant disease model (*in vitro* cell culture, computational/in-silico, *in vivo*/pre-clinical animal model) is essential (Noble and Burns, 2010a). Currently, genetically modified rodent models are available to study neurodegenerative disorders. Although these pre-clinical *in vivo* models are advantageous, the degree to which they can lead to human translation and provide us with data that closely matches human diseases varies greatly. Clinical study of neuroprotective agents in humans is challenging as such research investigation would prove high-risk, expensive, and extremely time-consuming without easily measurable outcomes. Without a reproducible and informative model system of neurodegenerative disease (e.g., including multiple cell types in addition to mature neurons), the invention of novel therapeutic strategies will repeatedly stall (Yiannopoulou and Papageorgiou, 2013). Similarly, existing therapies for most neurodegenerative diseases are symptomatic, and a few disease-modifying therapies are available. On a positive note, over the last few years, there has been remarkable progress in understanding the triggers and targets of neurodegenerative disease, motivating researchers to develop new promising disease-modifying therapy for effectively managing NDs (Noble and Burns, 2010b). Identifying specific molecular targets has led to the development of novel therapeutic approaches. Gene therapies, including CRISPR-Cas9 editing and RNA interference, hold promise in addressing genetic mutations underlying neurodegenerative disorders. Targeting protein aggregates, such as beta-amyloid in Alzheimer's or alpha-synuclein in Parkinson's disease, is another area of active investigation (Nojadeh et al., 2023). Small molecules, antibodies, and vaccines designed to modulate these pathological proteins are progressing through preclinical and clinical trials, offering hope for effective disease-modifying treatments. Understanding the in-depth cellular and molecular mechanisms of neurodegenerative disease progression is the initial step in designing effective neuroprotective strategies. The second step is validating and testing promising neuroprotective or neurorestorative agents, which both involve rigorous monitoring of retinal ganglion cells and neurons in the brain (Yiannopoulou and Papageorgiou, 2013). The role of neuroinflammation in neurodegenerative disorders is gaining prominence. Microglial activation, astrocyte reactivity, and the release of pro-inflammatory cytokines contribute to disease progression. Immunotherapeutic strategies aimed at

modulating the immune response in the central nervous system are being explored. Monoclonal antibodies targeting inflammatory mediators or promoting immune clearance of pathological proteins are among the innovative approaches with potential clinical impact.

Advancements in neuroimaging, wearable devices, and biomarker identification are transforming the diagnosis and monitoring of neurodegenerative disorders. Functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and advanced bioinformatics enable early disease progression detection and tracking (Risacher and Saykin, 2021). Wearable sensors continuously monitor movement patterns, providing valuable data for early diagnosis and treatment evaluation. Additionally, identifying reliable biomarkers in cerebrospinal fluid and blood holds promise for non-invasive diagnostic and prognostic tools. The future of neurodegenerative disorder research is optimistic, and its success depends upon the multidisciplinary approach, incorporating genomics, proteomics, immunotherapy, and innovative technologies. As our understanding of the intricate mechanisms of degeneration deepens, so does the potential for targeted and personalized therapeutic interventions. The ongoing collaboration between researchers, clinicians, and industry partners and optimum funding from the government, philanthropic, and industries is essential to translating these promising advancements into clinically relevant treatments, ultimately improving the lives of individuals affected by neurodegenerative disorders.

8. Conclusion

The incidence of NDs is increasing, and despite novel findings to advance our knowledge on understanding of disease progression, there is a lack of potential neuroprotective and neurorestorative therapeutics creating an urgency for novel drug development. Advancement in understanding intra and inter-cellular signaling pathways and various targets involved in neurodegenerative disease help manage neurodegenerative disorders. Further neurodegenerative diseases studies must focus on improved drug delivery methods and critically understanding the pathophysiology of diseases, emphasizing the connection of various factors such as genetic alteration, inflammation, and other neurochemical anomalies. As the world population of aged individuals is increasing and so is the incidence of neurodegenerative disease, providing patients with effective strategies to treat or prevent neurodegenerative disease is a significant challenge that scientists, clinicians, and health authorities are facing. Solving this challenge effectively depends

on a clear understanding of the pathological events across the entire spectrum of neurodegenerative diseases, including diseases of the brain and the visual system. Future research should focus on associating molecular mechanisms with multifaceted neurodegenerative disease and exploring various methods "not limited to pharmacological agents" to manage and treat NDs effectively.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- Advancement in nanotechnology is a boon for cellular repair in mental disorders.
- Molecular mechanisms in NDs could augment mental illness therapies and research.
- Clinical insights may improve understanding of limits and benefits of NDs therapies.