# NEURODEGENERATIVE DISEASES:
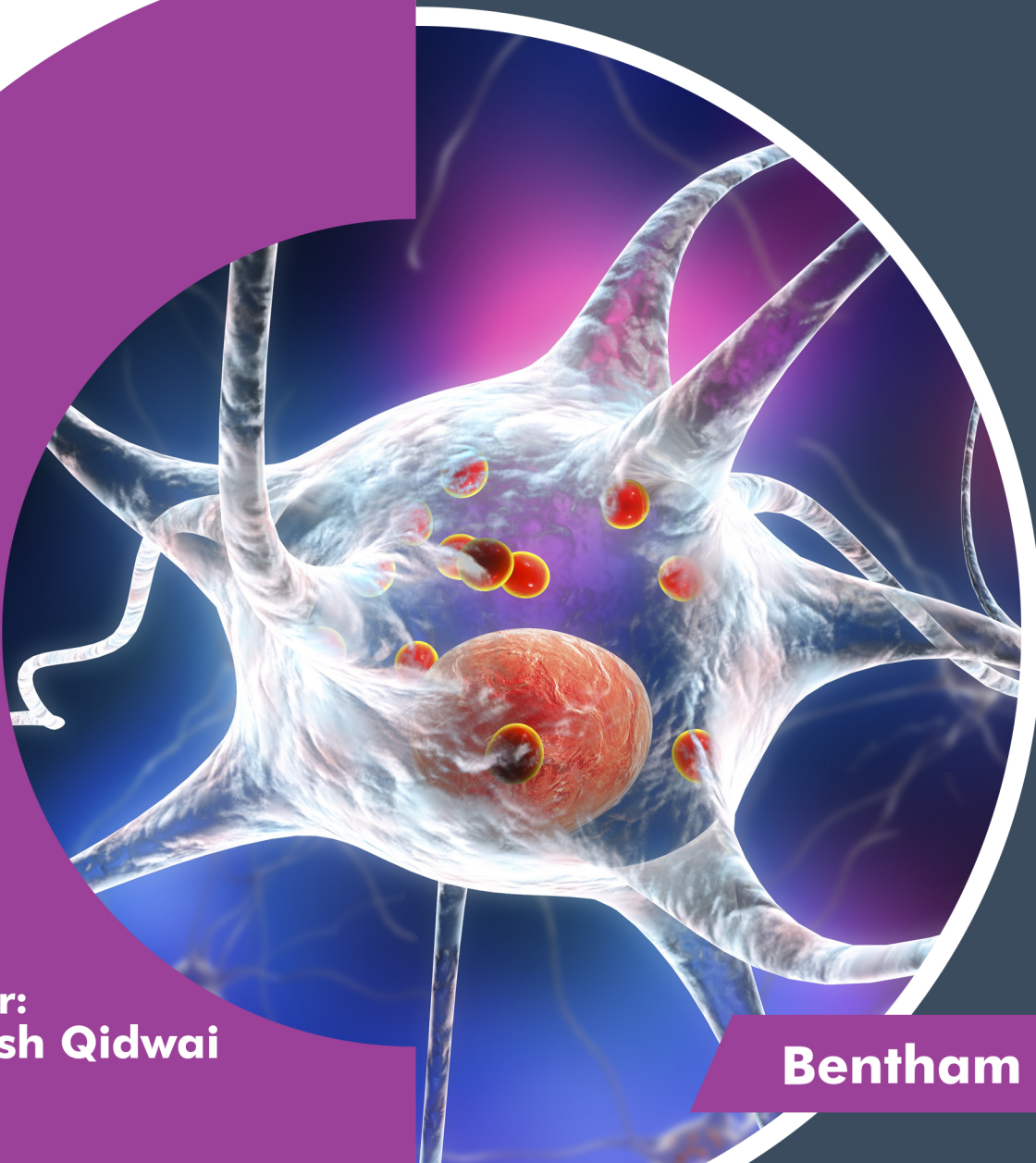# MULTIFACTORIAL DEGENERATIVE PROCESSES, BIOMARKERS AND THERAPEUTIC APPROACHES
# FIRST EDITION

**Editor:**
**Tabish Qidwai**

**Bentham Books**

# Neurodegenerative Diseases: Multifactorial Degenerative Processes, Biomarkers and Therapeutic Approaches

# (First Edition)

Edited by

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**Neurodegenerative Diseases: Multifactorial Degenerative Processes, Biomarkers and Therapeutic Approaches (First Edition)**

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# PREFACE

There are fourteen chapters in this book entitled " Neurodegenerative Diseases: Multifactorial Degenerative Processes, Biomarkers and Therapeutic Approaches." The book focuses on the current trends in pathophysiology, biomarkers, and therapeutic approaches for neurodegenerative diseases.

The goal of this book is to give readers an overview of multiple degenerative mechanisms in neurodegeneration, as well as biomarkers and therapeutic possibilities. The book is aimed to target students, research scholars, and neuro physicians who are interested in the topic. The book's structure is well-organized and updated.

This book is divided into three sections, each of which covers a different facet of the disease. Part I, which contains four chapters, is about multifactorial degenerative processes in neurodegenerative diseases; chapter 1 by Tabish Qidwai discusses multifactorial degeneration and the role of genetic and environmental factors in neurodegenerative diseases.

Sarika Singh *et al.* in chapter 2 outline the role of mitochondrial dysfunction. Chapter 3 by Mishra *et al.* presents the role of protein aggregation in neurodegenerative diseases. In chapter 4, Prakash *et al.*, describe the reactive oxygen species in neurodegenerative diseases.

Part-II is focussed on pathophysiology, and biomarkers in neurodegenerative diseases. This part consists of six chapters; molecular biology, pathophysiology, and biomarkers of Parkinson's disease are discussed in chapter 5 by Arshad *et al.* In the chapter 6, Yadav *et al.*, discuss the molecular basis, pathophysiology and biomarkers of Alzheimer's disease. Chapter 7 by Siddiqui reviews the molecular basis, pathophysiology and biomarker of Huntington's disease. Prakash *et al.*, in chapter 8, describes the molecular biology, pathophysiology and biomarkers of multiple sclerosis. Chapter 9, by Subhadip Chakraborty, discusses the molecular diagnostics and immunological markers of neurodegenerative diseases. In chapter 10, Dinesh Yadav describes the omics approaches for biomarkers investigation in neurodegenerative diseases.

Part-III of the book covers the therapeutic approaches for neurodegenerative diseases, this part consists of four chapters; In Chapter 11, Rajesh Ugale focuses on emerging therapeutic approaches for neurodegenerative diseases. Chapter 12 by Singh *et al.*, reviews the role of medicinal plants and natural compounds as antiparkinson agents. In chapter 13, Bandana outlines the neuropharmacology apporach in Alzheimer's and Huntington's disease. The last chapter by Vandana *et al.*, describes the description of public health and the burden of neurodegenerative diseases.

This book, I believe, will be of tremendous interest to students, doctors, researchers, and even patients and their families. Finally, I would like to express my gratitude to all of the contributors to this book, as well as the Bentham Publishing Editorial Board for providing us with this invaluable opportunity.

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**CHAPTER 1**

# Neurodegenerative Diseases Involve Multifactorial Interplay of Genetics and Environmental Factors

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**Abstract:** Neurodegenerative diseases are one of the leading causes of morbidity and disability worldwide, afflicting millions of individuals. These diseases emerge as a result of multiple factors, sharing pathogenic pathway that includes mitochondrial dysfunction, misfolded protein aggregation, and oxidative stress. Genetic and environmental factors have been identified to play a key role in neurodegeneration and modifying the risk of the disease. The association of neurodegenerative diseases to genetic factors and environmental agent's exposure is not well conclusive. As a consequence, studying the interplay of genetic and environmental factors in neurodegenerative diseases can help researchers better understand gene and therapy and disease progression. In this chapter, an attempt has been made to discuss the multifactorial degenerative process and the role of genetic and environmental factors in common neurodegenerative diseases. Understanding the mechanisms of disease initiation and progression is crucial for disease prevention and modification of disease risk. These information would be helpful in the exploration of therapeutic options against these diseases.

**Keywords:** Environmental factors, Genetic factors, Multifactorial, Mitochondrial dysfunction, Neurodegenerative diseases, Protein aggregation, Reactive oxygen species, Risk of disease, Therapeutics.

## INTRODUCTION

Neurodegenerative diseases are the leading cause of morbidity and disability. Researchers are giving special attention to these diseases as they impose a considerable socioeconomic impact. Millions of people throughout the world suffer from neurodegenerative diseases. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are all common neurodegenerative diseases. These diseases result in a variety of

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illnesses with varied etiologies and morphological and pathophysiological characteristics. The most commonly reported neurodegenerative diseases are Alzheimer's and Parkinson's diseases, which rank first and second, respectively, among neurodegenerative diseases. Over the course of its five-year plan, the World Health Organization (WHO) has adopted a specific push for Mental Health, with the goal of increasing treatment coverage for mental health problems for one hundred million additional individuals [1]. It has been identified that abnormal protein dynamics, including incorrect protein breakdown and aggregation, oxidative stress and free radical formation, bioenergetic impairment, and mitochondrial malfunction are all factors that contribute to neurodegenerative diseases. Aggregation and deposition of misfolded proteins, oxidative stress and mitochondrial dysfunction cause deterioration of the central nervous system [2].

Neurodegenerative disorders are multifactorial disorders including the interplay of aging, genetics and environmental factors. Genetic and environmental factors have been shown to play a key role in neurodegenerative diseases. The role of genetic factors is central to the etiology of neurodegeneration. Identification of disease genes and risk loci has contributed a lot to medicine. Genome wide association studies have increased our knowledge of the genome and the genetics of neurodegenerative disease. Studies have identified that genetics is targeting to find new disease-modifying therapies for neurodegenerative diseases. Certain genetic polymorphisms and increasing age are identified as risk factors for neurodegenerative disease. Other likely reasons might comprise gender, oxidative stress, inflammation, stroke, hypertension, diabetes, smoking, head trauma, and chemical exposure. In addition to this, exposure to metal toxicity and pesticides are responsible for the appearance of neurodegenerative diseases, we should focus on environmental factors in these diseases [3]. The pathogenesis of many of these diseases remains unknown. The association between environmental agent's exposure and neurodegenerative diseases is not well explored and conclusive. Besides, the role of genetic factors in neurodegenerative diseases is not investigated quite well. Exploration of genetic factors and environmental factors would be important in the identification of risk factors and effective therapeutics in neurodegenerative diseases. This chapter covers the genetic and environmental factors associated with neurodegenerative diseases. Moreover, the multifactorial nature of diseases has been covered.

## NEURODEGENERATIVE DISEASES INVOLVING MULTIFACTORIAL DEGENERATION

Neurodegenerative diseases such as AD, PD, HD and ALS, *etc.* are multifactorial in nature. They rely on a common pathogenetic mechanism involving aggregation and deposition of misfolded proteins, oxidative stress and mitochondrial

dysfunction leading to the deterioration of the central nervous system [2]. Identification of the basic etiology of these diseases would be important in therapies against them. Despite the fact that each disease has its own molecular mechanism and clinical manifestations, several common pathways may be found in various pathogenic cascades [2]. Neurodegenerative diseases are multifactorial degenerative process, hence interplay of several factors have been evidenced (Fig. **1**). Misfolding and non-functional protein trafficking are the causes of diseases including Alzheimer's, Parkinson's, and Huntington's. Moreover, mitochondrial dysfunction, oxidative stress, and/or environmental factors have shown a strong association with age implicated in neurodegeneration. Mutations in several human genes have been associated to neurodegenerative diseases.
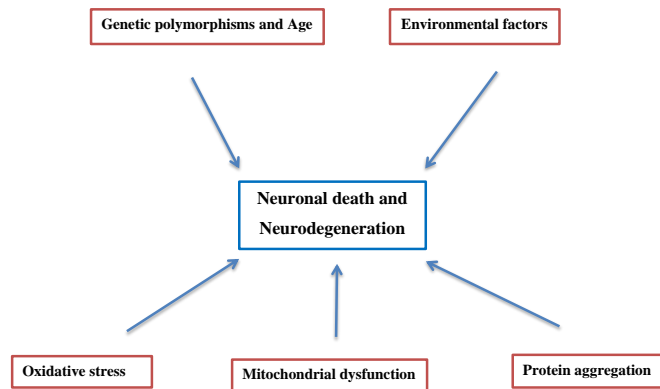


**Fig. (1).** This Fig represents the factors associated with neurodegenerative diseases.

## Protein Misfolding and Aggregation in Neurodegenerative Diseases

Stable conformation of the protein is necessary for the biological function of the protein. Protein folding is a complex process, guided by a molecular chaperone. Protein folding is linked to gene transcription, protein biosynthesis, post-translational modifications, ubiquitin-proteasome system destruction, and autophagy. Disturbance in protein homeostasis will lead to protein misfolding this is the pathogenic underpinning of the most neurodegenerative diseases. Misfolded proteins frequently aggregate and accumulate, producing neurotoxicity and causing neurodegenerative diseases [3, 4].

## MITOCHONDRIAL DYSFUNCTION IN NEURODEGENERATIVE DISEASES

Cell death is a key feature of neurodegenerative diseases which is centrally regulated by the mitochondria. A key role of mitochondria has been identified in ageing-related neurodegenerative diseases [4]. Mitochondrial DNA mutation and

# Colligation of Mitochondria Dysfunction and Neurodegeneration: Parkinson's Disease

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**Abstract:** Parkinson's disease (PD) is a first most common motor neurodegenerative disorder and caused due to degeneration of dopaminergic neurons of nigrostriatal pathway of brain. Brain is the most active organ of human body which receives, process and command the responses utilizing approximately twenty percent of body's total energy. Mitochondrion is the cellular powerhouse produces ATP by utilizing various complexes of electron transport chain. This ATP is the energy source of cells and is being used for physiological functions of the cells, indicating the critical role of mitochondrial functionality in cellular physiology. In PD pathology the impaired bioenergetics is the known and critical factor which essentially requires for cellular physiological responses and failed to maintain it will lead to self-destruction of cell, termed as apoptosis. Neuronal apoptosis is the inescapable event in PD pathology and suggest the implications of cellular bioenergetics and the close conjunction of mitochondrion functionality and disease pathology. In this chapter mitochondrion functionality and its correlation with various neurodegenerative signalling pathways during PD pathology will be discussed.

**Keywords:** Mitochondrial dysfunction, Neurodegeneration, Parkinson's disease (PD), Pathology.

## INTRODUCTION

Parkinson's disease (PD) is the most common motor neurodegenerative disease characterized by preferential loss of dopaminergic neurons of the nigrostriatal pathway that leads to the dopamine deficiency in the substantia nigra (SN) and striatum regions of brain. In spite of research of several decades the information regarding disease onset and its pathological markers is limited. Among known pathological marker the presence of Lewy bodies containing α-synuclein, an

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intracellular protein, is well accepted in PD pathology [1]. In regard to symptoms, PD pathology exhibit both motor and non-motor symptoms. The classical parkinsonian motor symptoms include bradykinesia, resting tremor, rigidity and postural instability [1]. The non-motor symptoms include sleep disturbances, depression, cognitive deficits, and autonomic &sensory dysfunction which may be psychological effects along with specific effects of disease onset [1]. In spite of the advancing research on the PD pathology, the exact cause and mechanism behind the PD pathogenesis is still mysterious and need further evaluations. To date various etiological reasons have been suggested by the researchers to be implicated at both cellular as well as genetic level in the disease pathology but still lacunae exist. The concept of mitochondrial dysfunction in PD pathology was identified in 1980s with unwanted generation of 1-methyl-4-phenyl-1,2-5,6-tetrahydropyridine (MPTP) during synthesis of heroin. MPTP itself is not toxic but able to cross the blood brain barrier and in brain processed with enzyme monoamine oxidase B (MAO-B) to form the toxic cation 1-methyl-4-phenylpyridinium (MPP+). MPP+ is toxic to brain cells as it is selectively taken up by dopaminergic cells and inhibits multiple complexes of the respiratory chain [2] therefore, inhibiting the ATP synthesis or mitochondrial functionality. This finding of 1980s is still significant as MPTP is still being utilized to induce the PD pathology in rodents to understand the disease mechanisms [2].

While considering the genetic aspects, PD can be caused by mutations in genes identified by linkage analyses that are inherited in an autosomal recessive or dominant manner. Mutations in the genes encoding α-synuclein and LRRK2 (leucine-rich repeat kinase 2) are responsible for autosomal dominant forms of PD, presumably by a gain-of-function mechanism. Other mutation implies to loss-of-function which involve mutations in the genes encoding Parkin, PINK1, and DJ-1, which cause functional impairment of mitochondrion and mediates the autosomal recessive PD [1]. Such PD associated functional impairment of mitochondrion caused significant progressive damage to neurons involving various signaling mechanisms mostly involving the ATP driven mechanisms. The major mechanisms which have been investigated in disease pathology are oxidative stress, protein aggregation and degradation mechanisms, compromised protein synthesis and trafficking, alterations in mitochondrial dynamics, affected calcium homeostasis, defective autophagy, DNA damage and initiation of cellular death pathways. In the following section we are focusing on mitochondrial functionality in PD pathology and its correlation with other neurodegenerative signaling pathways during disease pathology.

## ROLE OF MITOCHONDRIA IN PD PATHOLOGY

Mitochondria are double membrane bound organelles found in most of the cells of eukaryotic origin. These are the key organelles that produce most of the cellular energy required for the proper functioning of the cell, also known as the "power house of the cell". The energy production in mitochondria mainly occurs through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS). The electron carriers that generated in TCA cycle contribute their electrons to the electron transport chain (ETC). The OXPHOS consists of four distinct multisubunit complexes (I-IV) and two electron carriers that generate a proton gradient across the mitochondrial inner membrane, which in turn drives ATP synthase (complex V) to generate ATP. The production of ATP is based on the movement of electrons between the complexes and the transport of the protons from matrix to intermembrane space which generate a proton concentration gradient used by the ATP synthase for ATP production. Complex I and III are the centres that give rise to the reactive oxygen species (ROS) including oxygen radicals and hydrogen peroxides during ATP generation. Both complex I and III of ETC can be leaky and leaked electrons may react with the oxygen present in the mitochondrial matrix to form superoxides. Under physiological conditions these free radicals which generate as side products during ATP synthesis, can be abandoned by the available cellular antioxidants however, during pathological conditions the antioxidants level gets depleted thus these free radicals could not be abandoned and may initiate the pathological signalling mechanisms. In neurons, the glycolytic pathway is limited and the energy production is mainly dependent on mitochondria. These mitochondria are mainly present at the synapse, where the energy demand is quite high. It can be move from a presynaptic region to the postsynaptic region of a neuron according to cellular demand of ATP which further reveals the inevitable role of mitochondria in energy biogenesis in neurons. Physiologically mitochondrion that produces ATP actively, lowers the proton motive force, NADH/NAD$^+$ ratio and ROS production. Conversely the ROS production at complex I is increased by the low ATP production due to impaired respiratory chain. The reduction in the ATP production is an expected complication of defective mitochondrial respiration. This has been proved in MPTP induced experimental models of PD that ATP synthesis gets depleted by twenty percent in brain and also in synaptosomal & hepatocyte preparations [3]. Simultaneously, in other article it has been argued that depletion of more than fifty percent of complex I activity cause a significant reduction of ATP production in nonsynaptic brain mitochondria. In PD patients approximately twenty to thirty percent reduction in complex I activity has reported which caused significant ATP depletion and consequent impairment of neuronal physiology [3]. However, another report showed that mutation (A53T mutation) in α-synuclein in rodents also exhibit the mitochondrial dysfunction

# Protein Aggregation in Neurodegenerative Diseases

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**Abstract:** Protein aggregation-related diseases primarily affect the central nervous system and are involved in the pathogenesis of multiple neurodegenerative diseases as well as several rare hereditary disorders that involve the deposition of protein aggregates in the brain. These diseases include Alzheimer's, Parkinson, Huntington's disease, Prion diseases, amyotrophic lateral sclerosis, familial amyloid polyneuropathy, *etc.* The aggregates usually consist of fibers containing misfolded protein with a beta-sheet conformation. As a result, proteins' secondary structures change from α-helix to β-sheet, leading to the accumulation of harmful misfolded protein aggregates in the CNS. The misfolding, subsequent aggregation and accumulation of proteins in neurodegenerative diseases lead to cellular dysfunction, loss of synaptic connections and brain damage. This chapter discusses some of the important neurodegenerative diseases resulting from protein misfolding and explains the pathological mechanisms behind brain damage.

**Keywords:** ALS, Alzheimer, Amyloid beta, Huntington, Misfolding, Parkinson, Protein aggregation, Protein folding.

## INTRODUCTION

Proteins are one of the most predominant and essential macromolecules in living organisms. They are made up of one or more long chains of amino acids (the building blocks of proteins). Amino acids are simple organic compounds with an amine group (NH3), a carboxylic acid group (R-C(O)OH), and a variable side-chain specific to each amino acid. Every single component of our bodies, from hair to the toe nail, is made up of protein [1]. The human genome contains over 30,000 different proteins, which all contribute significantly to diverse biological activities such as catalysis, signal transmission, structural integrity, immune protection, transmission of nerve impulses, storage and transportation of nutrients,

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as well as regulation of growth and differentiation processes [2]. These remarkable arrays of functions result from proteins' unique ability to fold instantaneously into precisely determined three-dimensional conformation, which establishes functional diversity among protein molecules and allows them to interact with one or more multifaceted molecules, which leads to the formation of an efficiently functioning protein with a native fold [3, 4]. Folding of protein molecules starts as soon as the proteins are synthesized at ribosomes and successively passes through post-translational modifications to attain their functional and native fold [5]. Even though some proteins fold spontaneously as soon as they are synthesized, many proteins exhibit erroneous folding and are susceptible to misfolding [6]. Protein misfolding is a term used to describe a process in which proteins fold into completely erroneous or non-native conformational states [7]. It is a common cellular event that can occur at any time during a cell's life and is triggered by a variety of factors such as somatic or genetic mutations, inaccurate transcriptional or translational mechanism, disrupted folding and molecular chaperones machinery, erroneous post-translational modifications, as well as structural alterations due to certain environmental factors *viz.* pH, temperature, oxidative stress and presence of metal ions [8, 9]. Upon protein misfolding, aberrant exposure of hydrophobic surfaces drive proteins to aggregate, which in turn impairs normal cellular activities by entrapping functional proteins, supporting a malfunctioning cascade, and influencing the aggregation propensity of other protein species [10, 11]. The process of protein aggregation occurs when folding intermediates, partially folded or unfolded structures expose their hydrophobic core that is normally hidden in the native conformation. Protein aggregation is primarily driven by hydrophobic forces, which begin with the self-assembly of smaller misfolded monomers to produce a wide variety of folding intermediates known as soluble misfolded oligomers [12]. These misfolded oligomers are referred to as *"aggregation nuclei"* or *"precursor cores"* of protein aggregation because they provide a structural framework for the reversible attachment of other misfolded proteins to the growing core and assemble to form insoluble aggregates in the form of amyloid fibrils or amorphous aggregates (protein aggregates without amyloid fibrils) [13 - 17]. The mechanism of protein aggregation is influenced by a number of factors such as high hydrophobicity range, the proclivity to form β-sheet-rich structures, and low net charge states [18, 19]. Therefore, protein folding and unfolding are fundamental mechanisms for initiating and suppressing certain types of cellular activities. Moreover, folding and unfolding processes are extremely necessary for activities like translocation, trafficking, secretion, immunological responses, and cell cycle regulation [20]. As a result, an inability to fold accurately or to remain correctly folded will result in the dysfunction of cellular structure and function, leading to a variety of diseases [21, 22]. Many protein aggregation-related

diseases primarily affect the central nervous system (CNS) and are involved in the pathogenesis of multiple neurodegenerative diseases (NDs) as well as several rare hereditary disorders that involve the deposition of protein aggregates in the brain [23]. Aberrant proteins that are most commonly involved in the pathophysiology of NDs include amyloid-beta (Aβ) in Alzheimer's; neurofibrillary tau tangles in Alzheimer's, corticobasal degeneration, progressive supranuclear palsy, frontotemporal dementia, argyrophilic grain disease, and chronic traumatic encephalopathy; alpha-synuclein (α-Syn) in Parkinson, multiple system atrophy, and dementia with Lewy bodies; TAR DNA-binding protein 43 (TDP-43) in amyotrophic lateral sclerosis and frontotemporal dementia; prion proteins (PrPs) in prion diseases, Creutzfeldt-Jakob disease (CJD); huntingtin (Htt) protein in Huntington's disease; and transthyretin (TTR) protein in familial amyloid polyneuropathy (Table **1**) [15]. There are no evident commonalities among these disease-associated proteins in terms of expression level, size, sequence, structure, or function. Nevertheless, in diseased brain regions, all of these proteins misfold from their native states to construct intermolecular β-sheet-rich configuration ranging from small misfolded oligomers to large insoluble fibrillary aggregates [24, 25]. In this chapter, we addressed numerous scientific findings which indicate that a potential mechanism of neurodegeneration, involving protein misfolding and aberrant deposition of protein aggregates in neuronal cells is a prevalent cause of various neurodegenerative diseases. In addition, this section has also shed light on various neurodegenerative diseases, including Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis, and familial amyloid polyneuropathy, with an insight into their distinctive pathophysiology.

## PROTEIN AGGREGATION IN NEURODEGENERATIVE DISEASES

Millions of elderly populations worldwide suffer from neurodegenerative diseases, which cost millions of dollars a year to diagnose and treat. Unfortunately, the mechanisms underlying these disorders remain unclear, and no effective treatments are available. The pathogenesis of various neurodegenerative diseases, including Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis is nearly identical. Protein misfolding disorders, proteopathies, and protein conformational abnormalities are all examples of neurodegenerative diseases. Misfolding and aggregation of certain proteins, which are specific to each condition, occur in all disorders [26]. Protein aggregation is caused by misfolding of proteins, and the accumulation of protein aggregates is thought to be the cause of such neurodegenerative diseases. Genetic and environmental variables cause conformational changes in some native proteins in the brain (for example, prion, tau, β-amyloid, α-synuclein, and huntington). As a result, proteins' secondary structures change from α-helix to β-sheet, leading to the

# Role of Reactive Oxygen Species in Neurodegenerative Diseases

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**Abstract:** The altered redox state leads to oxidative stress through the extravagant synthesis of reactive oxygen species (ROS) and inhibition of the antioxidant system. The high oxygen demand in nervous tissue makes it vulnerable to ROS, and the presence of peroxidation-prone lipid cells worsens the situation. We now understand that oxidative stress plays a role in the pathophysiology of neurodegenerative diseases such as Parkinson's disease, Motor neuron disease, and Alzheimer's disease. In spite of the fact that there is no lasting cure for any of these diseases, antioxidant treatments have been promoted as ways to treat and discourse neurodegenerative diseases. However, the results regarding their efficacy are contradictory. This chapter examines the role played by oxidative stress in the etiology of neurodegenerative diseases and how they lead to brain dysfunction in people. It will later provide an overview of antioxidants as a therapeutic option for oxidative stress-induced damage.

**Keywords:** Alzheimer's disease, Motor neuron disease, Neurodegenerative disorders, Oxidative stress, Reactive oxygen species (ROS), Parkinson's disease.

## INTRODUCTION

In the partial oxidation of oxygen, reactive oxygen species (ROS) are produced, along with electrons coupled to outer shell orbits. These species generate free radicals by producing oxygen and generating free radicals. ROS originates from a variety of sources in the body, including endogenous and exogenous sources. The mitochondrial pathway consists of several mechanisms, including complexes of cytochrome P450 metabolism and inflammatory cascades. However, the xenobiotic pathway is a result of ionizing radiation, heavy metals, and smoking cigarettes [1, 2]. Oxidative stress is believed to be caused by a mismatch between

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the cellular antioxidant defense system and the generation of ROS. This entails an increase in the generation of waste as well as a decrease in the removal of waste. Unlike other molecules, ROS have increased reactivity in human cells and can react more quickly to similar and different molecules. Studies have shown that oxidative stress also modulates the cell cycle through the interaction of ROS with organic molecules [3]. Reactive oxygen species have been shown to contribute to apoptosis, oncogene expression, and cell signaling [4].

Neurodegenerative diseases are considered to be a complicated sum of disorders that show the feature of liberal expirations of neurons [5, 6]. However, the pathogenesis of neurodegenerative diseases has not yet been fully explored. However, enhanced oxidative stress has been suggested as one of the common etiologies associated with some neurodegenerative diseases. The result of oxidative stress is cellular impairment, DNA damage due to a dysfunctional repair system [7], and mitochondrial dysfunction. These symptoms collectively promote the process of aging thus accelerating the development of neurological disorders [8, 9]. Due to these hazardous symptoms of ROS, continuous efforts are being made for agents that protect against oxidative damage so that neurodegenerative diseases can be cured. As the focus of this chapter is on oxidative stress in the pathogenesis of neurodegenerative diseases, especially in motor neuron disease, Alzheimer's disease (AD), and Parkinson's disease (PD), oxidative stress is elaborated.

## WHAT ARE REACTIVE OXYGEN SPECIES?

*"Activating oxygen can produce compounds called radicals that put oxidative stress on cells. Such stress could ultimately lead to cancer and other diseases."*
*John Simon*

Reactive oxygen species form due to enzymatic reactions that involve NADPH oxidases, cyclooxygenase (COX), uncoupled endothelial nitric oxide synthase [eNOS], lipoxygenase, cytochrome P450 enzymes, and arachidonic acid and xanthine oxidases [10]. The mitochondria are the main source of ROS production. All three mitochondrial complexes - complex I, II, and III - release electrons that react with molecular oxygen and produce ROS. The superoxide dismutase 1 (SOD1) catalyzes the conversion of oxygen generated in the cytosol to $H_2O_2$ in the cytosol and mitochondrial intermembrane space [11, 12]. When $Fe^{2+}$ and $Cu+$ are reduced, OH is formed, causing oxidative stress-induced cell damage, which results in genome instability [13]. There are no specific types of cells that produce ROS; they are produced by all types of cells. Messages are transmitted intracellularly and intracellularly by them. Cellular response to ROS damage is influenced by signal context, stimulus intensity, stimulus duration, and stimulus

duration. ROS have been found to interfere with the signal transmission in the immune system, apoptosis, metabolism, aging, and hypoxia through alteration of morphology of signaling proteins through phosphorylation [14].

Additionally, ROS has been shown to enhance the signaling mediated by EGF and platelet-derived growth factors (PDGF), in which tyrosine kinase activity is enhanced by activating downstream signaling pathways such as PI3K-AKT and MAP kinase [15]. The increased level of ROS in cells leads to the following outcomes:

1. Oxidative stress

2. DNA and cell damage

3. Based on the severity of exposure it may also promote cell survival

4. Apoptosis

DNA is highly susceptible to mutagens, and ROS is known for its ability to induce stress through single-strand and double-strand breaks, point mutations, frameshift mutations, and DNA cross-links. Genome instability could result from apoptosis, replication errors, and apoptosis. Major ROS mutations include guanine alteration, resulting in G → T transversions [16]. The effects of ROS can be observed not just on DNA and apoptosis, but also on cancer initiation and progression [17], especially if the mutation involves oncogenes or tumor suppressor genes. Fig. (**1**) summarizes the effects of ROS on neurodegenerative disorders.
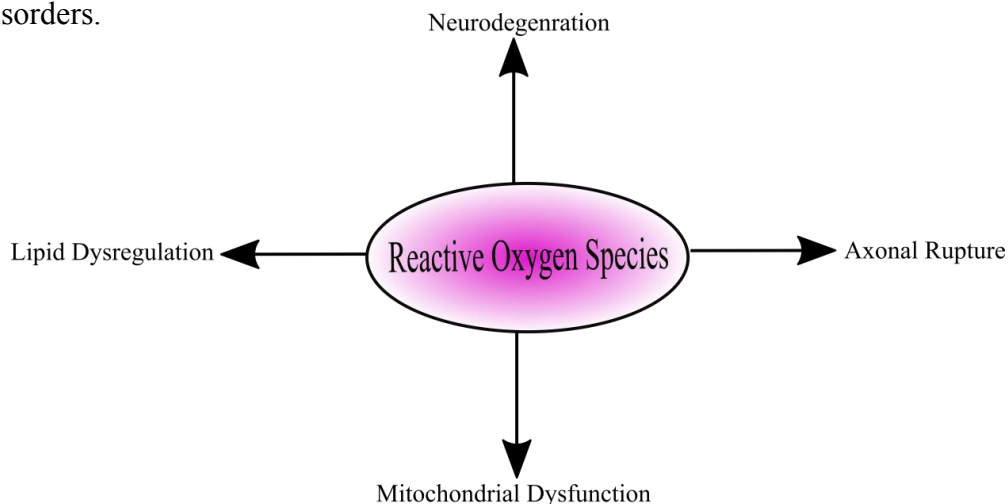


**Fig. (1).** Schematic representation of effects of ROS in neurodegenerative diseases.

# Parkinson Disease: Molecular Biology, Pathophysiology and Biomarkers

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**Abstract:** Parkinson disease is a progressive neurodegenerative disorder that affects motor control of the body. The disorder is associated with the loss of neurons due to formation of protein aggregates that leads to the development of apoptosis and degeneration of the neurons. The disease progresses slowly, making it difficult to identify it at early stage. But the availability of potential therapeutic biomarkers in analysis and early identification of PD is of great importance. The current review discusses here the molecular biology, pathophysiology and availability of potential biomarkers associated with the PD condition.

**Keywords:** Parkinson disease, Alpha synuclein, neurodegenerative disorders, motor control, Dopamine.

## INTRODUCTION

Parkinson's disease (PD), a neurodegenerative disorder of the central nervous system, affects motor control of the body [1]. The system most commonly affected in PD is dopaminergic neurons especially in substantia nigra and striatum [1, 2]. The dopaminergic system includes the dopamine neurotransmitter and the dopaminergic neurons, functioning to regulate motor activity, motivation as well as other related cognitive functions [3]. The disease is most commonly unidentifiable at an early stage as the symptoms appear at higher stages of the diseases [3]. So, there is a great requirement of a potential therapeutic biomarker for early detection and identification of the disease.

There are different types of PD biomarkers such as genetic biomarkers, biochemical biomarkers, clinical as well as imaging biomarkers. Most common PD biomarkers include dopamine and its related metabolites, amino acids, α-synuclein, proteomic biomarkers, *etc* [4, 5].

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Moreover, recent studies have incorporated new micro-RNA based biomarkers as well as metabolic biomarkers form the biofluids [6]. The current chapter discusses here some of these available biomarkers for the identification of PD.

## Parkinson's Disease (PD)

PD is a progressive long term neurodegenerative disorder that affects central nervous system and leads to continuous loss of dopamine (DA) neurons [3]. The loss of dopamine neuron is prominent in Substantia Nigra (SN) of the basal ganglia in midbrain and thus affects motor functions of the body [1]. Basal ganglia is involved in the regulation of motor function and in PD the loss of neuron cause aberration in movement, muscular rigidity, difficulty in walking and resting tremor [7, 8]. The disease affects almost 1% population worldwide which covers old age person with the age of 60 years or more [9, 10]. As the disease worsens, the non-motor functions are also affected in PD [8]. Later stage of the disease affects cognitive functions that develops in apathy, anxiety, stress as well as depressive disorders and dementia in people [7, 8]. The degeneration of the neuron is associated with the formation of Lewy bodies due to misfolding of proteins in neurons [11]. The aggregated misfolded protein causes neurodegeneration and ultimately the death of neurons [11, 12].

Although the main cause of the PD is not clearly known but the role of genetic and environmental factors has equal importance. Similarly, other risk factors include exposure to some pesticides as well as prior head injury. However, people with the habit of smoking tobacco and utilization of coffee and tea are known to have very low risk factor.

## GENETIC AND MOLECULAR BASIS OF PD

## Genetic and Epigenetic Factors of PD

The probability of PD with its genetic association is almost 15% of the PD patients, which shows its family history [12]. It has both an autosomal dominant and recessive types genetic association of the disease [12]. The studies have so far confirmed mutations in different genes associated with the PD including genetic polymorphisms [12]. Some of these genes includes α-synuclein, Parkin, DJ-1, VPS35, LRRK2, GBA1 and PINK1 whose mutation is found to be associated with the PD condition [13].

Altogether, the epigenetic factor also plays an important role with the pathophysiology of PD. The term epigenetic refers to the alterations in chromatin structure through histone and/ or DNA modification in such a way that does not cause any change in DNA sequence [14]. These epigenetic modification affects

the gene expression profile that results in altered cellular and molecular functions [14]. Such modifications are heritable and are also affected by the different environmental factors as commonly observed in sporadic PD condition [15]. The most common effect of environmental factors on such modification is observed in α-syn gene (SNCA) where methylation of CpG-2 island prevents the binding of the TFs to SNCA and subsequently inhibits the overexpression of α-syn [16].

**Environmental Factors of PD**

Different environmental factors also cause PD conditions which includes mainly toxins such as heavy metals. Heavy metals exposure causes dopaminergic neurons death in substantia nigra which further develops into PD [17]. These heavy metal exposure to neuronal cell causes higher level of oxidative stress inside cell [17]. The accumulation of heavy metal when present inside dopaminergic neurons increases the probability for PD [18]. The study has confirmed that the *in vitro* oxidation of dopamine in the presence of monoamine oxidase and oxygen generates 3,4-dihydroxylphenylacetaldehyde (DOPAL), which is very much involved in formation of oligomerisation of α-syn [19]. Moreover, monoamine oxidase inhibition results in an decreased DOPAL formation and further decreased oligomerization of α-syn in these neurons [19]. Similarly, dopamine autooxidation forms dourmine quinone (DAQ), which has the capacity to the formation of non-fibrillar α-syn oligomers and its further transmission to nearby neuronal cells [16].

The accumulation of cytosolic dopamine in dopaminergic neurons is prevented by the expression of neuromelanin pigment which is highly expressed in these neurons [20]. Thus, it prevents the formation of oxidative stress inside neurons. However, decaying neurons release neuromelanin pigment in extracellular fluid which activates neuroglia and in turn promotes neuroinflammation in nearby neurons [20]. In spite of this when this neuromelanin is associated with the lipid promotes the aggregation of α-syn into insoluble forms that leads to the progression of PD [20, 21]. Furthermore, genetic polymorphism in cytochrome P450 2D6 (CYP2D6) enzyme affects the metabolism of toxins, thus they are associated with the progression of PD [22]. The rodent study with CYP2D6 deficient animals exhibited higher level of oxidative stress and progression of PD when exposed to the pesticides (*e.g.*, organophosphates, atrazine) [22].

**Molecular Mechanism of PD**

Different cellular and molecular processes are involved in the progression of PD. The pathophysiology of the PD is mainly based on the fact that the neurodegenerative condition in dopaminergic neuron that causes impaired brain functions. Although there are different proposed mechanism for the PD

# Alzheimer's Disease: Molecular Biology, Pathophysiology and Biomarkers

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**Abstract:** Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the central nervous system and the leading cause of dementia in elder people. The clinical symptoms of AD are memory loss and cognitive dysfunction. Pathologically, AD is characterized by the deposition of β-amyloid plaques and neurofibrillary tangles of hyperphosphrylated tau protein in the brain and neurodegeneration. However, the cause of AD is not known. Various genetic and non genetic factors have been involved in the pathogenesis. The main genetic risk factor of AD is E4 allele of apolipoprotein E. Currently; no effective treatment is available for AD. Only two classes of drugs namely acetylcholinesterase inhibitor (Galantamine, Rivastigmine, Donepezil), and N-methy--D-aspartate receptor antagonist (Memantine) are available for AD treatment. These drugs have limited effectiveness and disagreeable side-effects in AD patients. This chapter focuses on the molecular biology, pathophysiology of the disease and various diagnostic and prognostic biomarkers for the management of AD.

**Keywords:** Acetylcholinesterase inhibitors, Alzheimer's disease, Biomarkers, β-amyloid, Neurofibrillary tangles, Neurodegenerative.

## INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disease and the leading cause of memory loss in older people. Recent reports from World Health Organization (2020) and World Alzheimer's Disease (2018) show that 50 million people have dementia worldwide and now it has speedily become an epidemic, with the number of cases predicted to be 152 million by 2050 [1, 2]. AD is characterized by three phases of symptoms. The first phase of symptoms is cognitive dysfunction which includes memory loss, executive dysfunction (*i.e.* loss of intellectual coordination skills and higher level planning) and language difficulties.

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The second phase of symptom includes psychiatric and behavioral disturbances (depression, delusions, hallucinations and agitation) conjointly known as non-cognitive symptoms [3]. Third phase symptoms include difficulties with performing daily activities of life. Alzheimer's disease symptoms progress from mild memory loss to severe dementia.

The exact molecular-mechanism of AD is still not known. Clinically, AD has many neuropathological indications, including the deposition of β-amyloid (Aβ) peptides in the extracellular matrix between neurons (known as senile plaques) [4, 5] the intracellular formation of neurofibrillary tangles (NFTs) arising from the accumulation of hyperphosphorylated tau protein in neurons, neuroinflammation, neuronal loss and oxidative stress [6].

The cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers along with some new clinical methods can help diagnose alive AD patients, however, initially, it was confirmed after death by post-mortem autopsy [7]. There is no cure for AD. The main treatment option for patients is to reduce the level of Aβ to stop or retard the progression of pathology of AD. Currently, one combined drug therapy (memantine plus donepezil), memantine (N-methy--D-aspartate receptor antagonist) alone and three drugs galantamine, rivastigmine, donepezil (different cholinesterase inhibitors) are available for clinical applications [8]. These drugs have limited treatment possibilities and unpleasant side-effects in AD patients. Recently, multi targeted directed ligands (MTDL) are widely used for the treatment of AD. These drugs have additional biological properties along with cholinesterase inhibition [9, 10]. Drugs having disease modifying characteristics and neuroprotective behavior properties are of greater interest for research. This chapter highlights the molecular mechanisms, pathophysiology of the disease and various diagnostic and prognostic biomarkers for the management of AD.

**Risk Factors for AD**

Many research studies have reported that increased age, hypertension, increased cholesterol levels, genetics, Down syndrome, smoking and alcohol use, lifestyle-associated problems such as obesity, Type-2 diabetes mellitus, coronary artery disease, and mild cognitive impairment contribute to an increased risk of AD [11]. The symptoms of AD at different progressive stages are shown in Table **1**.

**Table 1. Symptoms at different progressive stages of Alzhiemer disease.**

| Stage | Mild | Moderate | Severe |
|---|---|---|---|
| **Symptoms** | Memory loss (Dementia) Unexplained mood swings Language problems Personality changes Poor or decreased judgment Loss of initiative | Unable to learn/recall new information Disorientation to time and place Behavioral changes Disturbances in short-term memory Confusion, wandering, aggression, agitation Require assistance activities of daily living | Motor disturbances, Gait incontinence Problem with attention and spatial orientation Bedridden Unable to perform activities of daily living Long-term care needed |

## Molecular Genetics of AD Pathogenesis

Several studies have shown that two distinct misfolded proteins accumulate in the brain of AD patients. The first is β-amyloid (Aβ), which is a proteolytic cleavage product of amyloid precursor protein (APP) by β- and γ-secretases. One of the pathological characteristics of AD is the accumulation of Aβ into plaques and smaller oligomers [12]. An early-onset autosomal dominant genetic disease is known as Familial autosomal dominant (FAD). Three very familiar genes (*APP, PSEN-1,* and *PSEN-2)* are related <u>to</u> the FAD [13]. Many reports have confirmed that mutations in APP are correlated with hereditary FAD. In 2% of AD cases, the age of onset of FAD is less than 65 years [14]. Several clinical trials have been attempted for the reduction of Aβ production or clearance of Aβ through antibody therapies or small-molecule by direct or indirect targeting of this pathway [12, 15]. In AD, the second misfolded protein is tau which aggregates in cells in the form of neurofibrillary tangles (NFT). It is a microtubule-associated protein. The most common pathological feature in AD patients is cognitive decline [16, 17]. However, the majority of AD cases (> 98%) are sporadic, which do not involve mutations in the processing pathways of APP and the age of onset is more than 65 years [12]. In these AD patients, main risk factor is apolipoprotein (APO) E4 (genetic factors) along with age [12].

## Pathophysiology of AD

In AD patients, neuronal loss may be observed in the brain, mainly in the hippocampus, entorhinal cortex, amygdala and the cortical related areas and different cotices regions (frontal, temporal and parietal). Some pathological changes are also seen with cholinergic basal nucleus and the subcortical nuclei (*i.e.* serotonergic dorsal raphe, noradrenergic locus coeruleus). In addition, in the entorhinal and trans-entorhinal cortex, hippocampus (CA1 region) and the cortical

# Huntington's Disease: Molecular Basis, Pathophysiology and Biomarker

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**Abstract:** Huntington's disease (HD), a hereditary autosomal dominant neurodegenerative disorder is characterised by weak cognitive and motor functions. The symptoms most commonly prevail among 30-50 years age group people. The coordination and movement abilities gradually worsen, and mental abilities mostly decline that progress towards dementia. The basis behind the HD disease is neuronal death due to mutations in huntingtin (HTT) protein, a protein required for the development and survival of neurons. There is an increase in the number of CAG repeats that generally code for glutamine within the HTT gene, resulting in an expansion of polyglutamine chain in HTT protein. This mutated HTT protein is toxic causing neuronal death and motor dysfunction. There is no known therapy for this disease other than suggestive relief treatment approaches. The review will be discussing here the molecular mechanism, pathophysiology and the potential biomarkers associated with HD.

**Keywords:** CAG, HD, HTT, Huntingtin disease, Motor disorders.

## INTRODUCTION

Huntington disease is a progressive neurodegenerative disorder that causes impaired cognitive and motor function. It is an autosomal dominant type genetic disorder that passes from one generation to the next. The progression of the disease generally starts 15-20 years before the appearance of HD symptoms and the common age group being targeted by the disease is 30-50 years [1]. The prevalence of HD is almost 5–10 cases per 100,000 people worldwide irrespective to the race and ethnic group [2]. Till date, no clinically available therapeutic method is available that can specifically prevent HD. However, current strategies

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brain atrophy within striatum and cortical region that affects the diverse types of motor and cognitive functions [3]. In the severe stage of the disease, other brain regions are also affected by the disease.

The main molecular mechanism behind the progression of the disease is a mutation in HTT (Huntingtin) gene that forms a mutated protein mutHTT [4]. This mutated protein contains an increased number of CAG repeats ($\geq 40$), which forms a poly glutamate chain. Generally, in normal HTT protein, it contains only up to 20 repeats [5]. This mutHTT protein forms aggregate inside neurons and affects different neuronal functions including axonal transport. Altogether, this protein interacts with other proteins and alters their function. The modified functions in these neurons result in different types of anomalies that ultimately cause neuronal death (approximately 88% striatal neurons in HD patients) [6].

Generally, the disease progresses almost 15-20 years before the appearance of clinical symptoms of HD. Due to this, early detection of HD is almost impossible unless the family history of the disease is not known [7]. The studies are going on to find out a precise biomarker for mainly focus on delaying the progression of the disease. The HD patients containearly diagnosis of HD using different biological techniques. The current chapter reviews the involvement of potential biomarkers for diagnosis and early detection of HD.

## Huntingtin Disease

Huntington's disease (HD) is a progressive neurodegenerative disorder characterised by impaired motor, psychiatric and cognitive functions. It is an autosomal dominant genetic disorder that passes from one generation to another having a mutation in the huntingtin (HTT) protein located on small arm of chromosome number 4 [8]. Disease progression is generally between 30-50 years of age group with a frequency of almost 5-10 among 100,000 people worldwide [2]. The Juvenile HD which generally occurs before the age of 20 (almost 8% of all HD cases) generally exhibits the symptoms of Parkinson's disease with slow body movement [9, 10]. Major psychiatric and cognitive symptoms associated with the HD include suicide tendency, affective disorders, obsession, apathy, attention deficit, schizophrenia-like symptoms, lack of motor skills, impaired sleep cycle and weight loss. The basal ganglia are one of the most important brain regions affected by this neurodegeneration HD condition and result in increased movement disorder commonly known as chorea disorder [10]. With the passage of time the disease progresses and worsens the condition that the person faces dementia and difficulty in talking. The person with HD may further develop cognitive disfunctions such as anxiety, depression, mood swing, anger *etc*.

Other secondary diseases such as pneumonia, heart failure worsen the diseases condition with utmost probability that leads to the death of the person [10].

The mutant huntingtin protein causes neurodegeneration in the nervous system [5]. Currently, there is no therapeutic availability for HD but a few drugs such as tetrabenazine can be used for controlling movement and other difficulties.

## Genetic and Molecular Basis of Huntingtin Disease

The gene for huntingtin disease was first discovered in 1993. It is present in all persons with two copies on the homologous chromosome. The person with mutation in either copy of the homologous huntingtin gene develops HD. It is an autosomal dominant disorder which means a person with single mutated copy of the gene will have HD and the probability of a child having HD is almost 75% if both of their parents are carriers of the defective gene [5]. It is also independent of the sex of the individual and does not skip from one generation to the next generation. Generally, the huntingtin gene contains up to 20 repeats of trinucleotide CAG (CAGCAGCAGCAGCAG) but in mutated huntingtin gene of HD condition, the repeat extends more than 40 (CAG expansion) that causes a mutated protein (mHTT) formation and ultimately the neurodegeneration [11]. The extended CAG repeats cause misfolding of protein and it forms clumps within neurons leading to neuronal death [11]. The mutated huntingtin protein (mHTT) does not affect all brain parts equally as all neurons contain these mutated gene do not depend on this protein for their function. Moreover, the internal environment of neurons with this mutation and the effect of other interacting factors also governs the pathological condition. The most important brain part damaged in HD condition is the striatum, which is involved in vital functional and behavioural aspects of our brain such as movement and coordination, learning and memory, mood control, *etc* [12]. The huntingtin protein has an important function in neurodevelopmental stages. In mutated conditions, the huntingtin protein activates a number of cellular processes such as apoptosis, caspase activation, excitotoxicity, mitochondrial dysfunction, neuronal membrane damage, impaired axonal transportation *etc*. that ultimately leads to neuronal death [12] (Fig. **1**).

The trinucleotide repeats in huntingtin gene are not constant between all individual and in different generations. The trinucleotide repeats CAG code for the amino acid glutamine and by this mutation, it produces a mutated protein with an extended polyglutamate chain or polyglutamine tract (polyQ tract) and the part of the gene with this repeat is known as *polyQ* region [13] (Fig. **2**).

# Multiple Sclerosis: Molecular Biology, Pathophysiology and Biomarkers

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**Abstract:** In the brain, multiple sclerosis is a chronic disease caused by immune-mediated neurodegeneration. About 2.5 million people around the world suffer from multiple sclerosis (MS), and women are more prone to it. Neither clinical nor imaging biomarkers are used to diagnose or characterize the disease. Molecular biomarkers have been developed from immunology and neurobiology because they are well matched with causal path mechanisms and other disease characteristics, thus, limiting the number of molecular biomarkers used in clinical practice. Currently, the chapter discusses the attribute of flawless MS biomarkers and the challenges associated with developing newer biomarkers. The study also discusses the discovery of biomarkers from the blood and cerebrospinal fluid (CSF) that are useful for diagnosing MS, predicting its prognosis, and evaluating its therapeutic response and side effects.

**Keywords:** Axonal injury, Biomarkers of MS, Molecular aspects, Multiple sclerosis (MS), Neuronal inflammation, Neuropathology of MS.

## INTRODUCTION

Multiple sclerosis (MS) is an inflammatory, chronic disease of the central nervous system (Brain and Spinal cord). Neurons are composed of axons, soma (cell body), dendrites, and presynaptic terminals. A myelin sheath surrounds the axonal region of neurons. The myelin sheath plays an imperative role in the propagation of action potentials. MS occurs when the myelin sheath is attacked by the self-immune system (Fig. **1**), leading to the demyelination of neurons that results in communication problems between the brain and the rest of the body.

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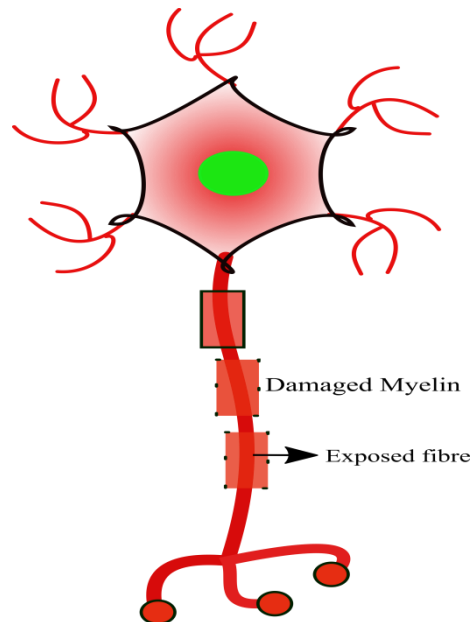
**Fig. (1).**  Represents the structure of a single neuron undergoing Multiple sclerosis. The axon fibre is demyelinated and thus hampering the communication between two neurons.

MS patients experience a wide range of symptoms. Despite this, fatigue and difficulty in walking are two of the most common symptoms of MS. Changes in the ability of daily routine performance and work done to lead to fatigue whereas walking difficulty may result from numbness in legs, difficulty balancing, weakness of muscles, muscle spasticity, vision problems, *etc*. Smoking is also a reason for the increased risk of multiple sclerosis development. Four types of multiple sclerosis on the basis clinical pattern have been recognised -

1. Relapsing-remitting multiple sclerosis (RRMS)
2. Primary-progressive multiple sclerosis (PPMS)
3. Secondary-progressive multiple sclerosis (SPMS)
4. Clinically isolated syndrome (CIS)

Among all of them, the most common type of MS is RRMS.

**Relapsing-remitting Multiple Sclerosis (RRMS)**

About 85% of patients with MS suffer from the RRMS. It involves the episodes of new or increasing symptoms, it is followed by periods of remission, during which symptoms can go away partially or totally.

### Primary-progressive Multiple Sclerosis (PPMS)

There is no relapse or remission of episodes and the symptoms become worse progressively. It occurs in about 15% of people with MS.

### Secondary-progressive Multiple Sclerosis (SPMS)

Initially, patients experience relapsing and remission episodes followed by the steady progressiveness of the disease.

### Clinically Isolated Syndrome (CIS)

It is the first episode of MS that lasts about 24 hours. Another occurrence of the episode leads to the RRMS.

### MOLECULAR ASPECT OF DISEASE

Till date, no specific test is developed for the diagnosis of MS [1]. The only possible method for diagnosis of the disease is based on symptoms developed by lesion studies. Lesions were created in different regions and different time points. The lesions are categorized as:

1. In the white matter of the CNS (the space dissemination criterion);
2. at least two distinct episodes in the disease course (the time dissemination criterion);
3. chronic inflammation of the CNS, as determined by analysis of the CSF (the inflammatory criterion).

The presence of any of these measures allows a general diagnosis of MS, which may be used according to the time course of the disease. An international board on the diagnosis of MS inferred that the time of diffusion criterion should be confirmed by clinical signs on MRI at least 3 months follow up or on a previous MRI.

To deduce an inference of MS, the physician must confirm the following given symptoms and biomarkers:

• discover evidence of injury in at least two discrete areas of the CNS that including the brain, spinal cord, and optic nerves.
• determine that the damaged areas developed at least 1 month apart.
• exclude all other possible diagnoses.
• observe that the symptoms remain present for more than 24 hours and occur as different episodes separated by 1 month or more.

**CHAPTER 9**

# Molecular Diagnostics and Immunological Markers of Neurodegenerative Disorders

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**Abstract:** Neurodegeneration is a progressive process that occurs with normal aging with accelerated loss of normal functioning and structure of neurons. The physiological aging of neurons can be expedited by many different factors like neurodegenerative diseases (NDs) including frontotemporal lobe degeneration (FTLD), Alzheimer's disease (AD), dementia with Lewy bodies (DLB), vascular dementia (VaD), *etc*. In the clinical view, the symptoms of different types of neurological disorders have a high degree of similarity, making it difficult for differential diagnosis. Clinicians need strong expertise to reach a correct diagnosis for a particular disease as there are so many established clinical guidelines for the diagnosis of different types of neurological disorders. Here, in this chapter, we shall focus to understand the different molecular diagnostic tools and immunological markers used for the detection of neurodegenerative disorders.

**Keywords:** Alzheimer's disease, BSE (Bovine spongiform encephalopathy), CJD (Creutzfeldt–Jakob disease), CSF (Cerebro Spinal Fluid), CWD (Chronic wasting disease), Dementia with Lewy bodies, FFI (Fatal familial insomnia), Frontotemporal lobe degeneration, GSS (Gerstmann– Stra ̈ussler–Scheinker syndrome), Immunology, Marker, Molecular diagnostics, Mutation, Neurodegeneration, Neurodegenerative diseases, PrPSc protein, Transmissible Spongiform Encephalopathies, Scrapie, Vascular dementia, vCJD (variant Creutzfeldt–Jakob disease).

## INTRODUCTION

Diagnostic tools are the critically and crucially important axis of our healthcare system. At present, the diagnostic results are the main axis to making a medical decision correctly. As for example, the high throughput genetic tests can be helpful in the arrangement of personalized cancer treatment or the customized microbial culture for the expression of targeted antibiotic combating a particular

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infection. Right diagnosis with proper diagnostics can provide detailed information at every stage of patient care, prevention, treatment and ultimately successful management of disease and health condition. Early detection and diagnosis could limit the progression of several neurodegenerative diseases. However, clinical diagnosis and management have been an intimidating challenge as the atypical complex nature and manifestations of these diseases. Among many, the main categories of diagnostics are molecular diagnostics, hematology, immunology, clinical chemistry, microbiology and many more [1]. Molecular diagnostics has dramatically transformed the diagnostic systems to such a great extent that leads to insights into research and treatment of various types of diseases with revolutionized health care.

In recent years, molecular diagnostics for neurodegenerative disorders have gained a particular recognition following the core of the disease pathogenesis which brings a successful diagnosis and treatment [1, 2]. Similarly, biomarkers are considered very important indicators of many normal and abnormal biological processes. Any pathological changes in genetics and biochemistries can give us comprehensive information regarding the nature of any kind of disease. Reliability, and precision are very much needed for choosing a good biomarker and it should have the capacity to distinguish between normal and particular diseases. It is proved that biomarkers have great potential in validating the chances of having a particular disease prior to its phenotypic expression (early diagnosis) and setting gold standards for the development of new ways for treatment [3, 4]. Normally, the growth of the tumour by the immune system is triggered by an antibody response against the neuronal antigens expressed by the neoplasm [5, 6]. This unfortunate assault due to the improper expression of immunological factors results in a rapid precipitation of a variety of neurological deficits and consequences [7 - 9]. Every level of the potentially damaged neurons is being technically considered as irreversible as the neurons lack the regenerative capacity. It is evident that neurodegenerative illnesses could be defined depending on the condition of their molecular characteristics before some particular symptoms significantly occur in later stages of the disease. Hence in this chapter, a rigorous effort has been made to understand the different molecular diagnostic tools and immunological markers used for the early detection of neurodegenerative disorders will be emphasized.

**What is Molecular Diagnostics?**

Laboratory medicine in developing countries ultimately depends on a collection of analytical tools commonly known as "Molecular Diagnostics." Although the term is undoubtedly familiar to many readers, the relatively new field and its continuous evolution leave many clinicians to make them uncertain of what some

molecular laboratory methods may be, their applications, underlying science, weaknesses, strengths, and most importantly—their utilities [10]. What are the uses of molecular diagnostics? Why is it used for?

Molecular diagnostics, the term is widely referred to as the detection of mutated or aberrant genetic/genomic variants, targeting to ease of sub-classification, diagnosis, detection, prognosis and monitoring response to therapy. All these factors contribute to the fine identification and characterization of the sporadic/complex basis of the any kind disease which is crucial for the accurate provision of diagnosis. Molecular diagnostics may be considered as a high-throughput tool with a fruitful interplay among laboratory medicine, genomics knowledge and technologies in the molecular genetics regime, especially with significant discoveries in the molecular genomic technologies field [11, 12]. Genome-wide association studies (GWAS) or next-generation sequencing are such a sophisticated methods that provide invaluable detailed insights into the progression of genetic diseases, and molecular biomarkers allow physicians to estimate the disease predisposition, design and establish accurate diagnostic methods and make customized options for therapy. Molecular diagnostics are increasingly used to guide patient management from diagnosis to treatment, mainly in the fields of neurological disorders, infectious diseases, cancer, congenital abnormalities and many more. Maintenance of good laboratory practices and regulatory adherence is crucial to the success of clinical genomics which can be challenging in the face of rapid growth, emerging technologies, and an evolving regulatory landscape. The rapid expansion of molecular techniques is due to the continuous increased high demand for genetic and genomic information for a particular disease or disorder [13].

## Molecular Diagnostics of Neurological Disorders and Diseases

Degenerative diseases of the nervous system impose huge medical and public health burdens on populations throughout the world. Neurological disorders may be defined as diseases that affect the brain, spine, and the nerves connecting to both of them. These disorders sometimes correspond to the disorders of brain nerves that are characterized by the gradual loss of neurons. Any kind of pathological changes in the neurons may cause malfunctioning and eventually result in the death of the neurons. There are no chances of rejuvenation as the neurons can not regenerate on their own after the neural deterioration or severe damage. Such disorders strike at the body's central and peripheral nervous system leading to many symptoms such as dementia, Alzheimer's disease, epilepsy and cerebrovascular diseases such as stroke, migraine, Parkinson's disease, multiple sclerosis and many more.

# Omics for Biomarker Investigation in Neurodegenerative Diseases

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**Abstract:** Neurodegenerative disease such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and the spinocerebellar ataxias is major health threat specifically in the elderly population. Currently, the disease diagnosis and progression is tracked through the clinical estimation which only gives a rough estimate of the disease severity. So the biomarkers serve as an essential tool in the disease diagnosis and disease progression. High-throughput omics-based technologies have facilitated the discovery of new biomarkers. The analytic methods underlying the basic omics-based technologies, genomics, transcriptomics, and metabolomics are now been extensively useful in the identification of novel biomarkers. These new candidate biomarkers are helpful in the clinical management of neurological disorders.

**Keywords:** Genomics, Metabolomics, Neurodegenerative disease, Omics, Proteomics, Transcriptomics.

## INTRODUCTION

Neurodegenerative disease is one of the major challenges affecting human health across the globe. It is an age-dependent disorder primarily affecting the elderly population, which has substantially increased in recent years [1]. The fact that this disorder is incurable is the main source of concern. It happens due to progressive degeneration and the death of the nerve cells. World Health Organization, the World Bank, and the Harvard School of Public Health (the Global Burden of Disease Study) in a collaborative study have revealed neurodegenerative disease to be a major public health issue and predicted it to be a major factor of concern for human health after cancer in 2050. These predictions are alarming and may pose serious health concerns, especially for the aging population. Some of the

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commonly occurring neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and the spinocerebellar ataxias.

Unlike most diseases, no clear diagnostic test is available that can detect the occurrence of neurodegenerative disease. Currently, only symptom-based screening is performed through specific neuroimaging which is considered to be time taking process often taking years for accurate prediction except in the case of genetic neuro disorders. The pathophysiology of most of genetic disorders is still unexplained. The potential mechanisms associated with the neurodegenerative disorders include protein aggregation, an anomaly in gene expression and transcription regulation, mitochondrial dysfunction *etc.*

## BIOMARKERS IN NEURODEGENERATIVE DISEASE

An effective strategy is needed to design tools for the detection of neurological disorders, and in this direction, the development of efficient biomarkers could be targeted using technological innovations in health sciences. Due to the lack of effective analytical methods, most neurological disorders are clinically misdiagnosed. Newer, reliable methods may provide biomarkers specific to these diseases and could be utilised for accurate diagnoses and thus would be useful in treatment interventions. Biomarkers are generally elements associated with specific indicators corresponding to different parts of the body such as blood, saliva, urine and cerebrospinal fluid (CSF). These indicators are useful tool for estimation of physiological or pathological conditions linked to clinical manifestations of any disease [2]. Owing to their usefulness in the neurological disorders they have great societal as well as medical significance [3, 4].

Biomarkers are used for disease diagnosis at an early stage. Moreover, it can detect disease progression and efficacy of the administered drugs. An ideal biomarker should be easy to detect and quantify. It should have stability and reproducibility, and should not be affected by disease factors. Biomarkers can be identified by imaging, neurophysiology, and also by the advent of recent omic-based techniques. The high-throughput omics technologies are well suited for biomarker discovery. It helps in detailed bioanalysis of the molecular samples, even at very low concentrations. The final application of developed biomarkers needs clinical validation to confirm the candidate biomarker in diagnosis and disease progression.

The biomarkers for any disease may be used for any of the three below mentioned approaches:

1. Diagnostics

2. Measurement of disease severity

3. Assessing motor and non-motor prognosis.

Several omics -based approaches have been applied for the biomarker discovery in the neurological disorders. Genomics, proteomics and metabolomics along with the tools in each omics approach and the recent reports have been discussed in detail. Overview of all the omics approach and associated techniques for biomarker discovery is shown in Fig. (**1**).
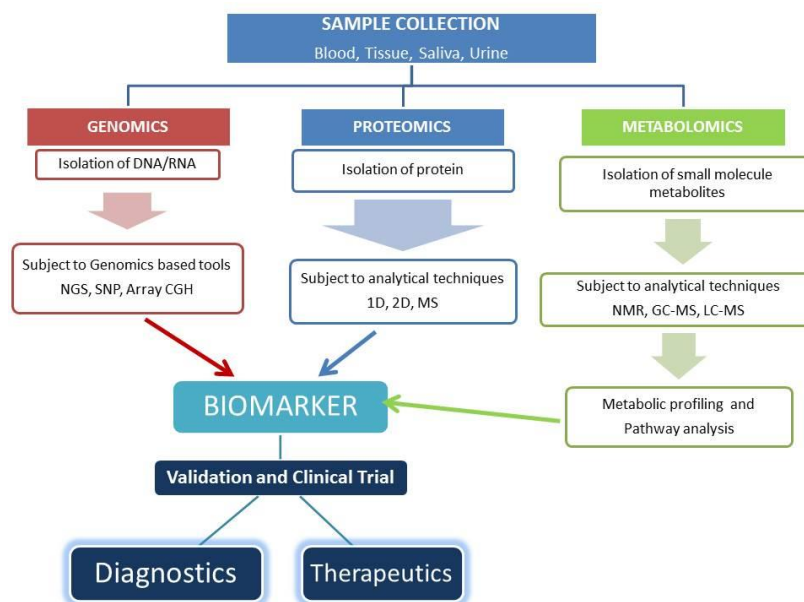


**Fig. (1).** Schematic representation of Omics-intervention in biomarker development.

## GENOMICS

It deals with the analysis of the whole genomes of any organisms like human genome. Lately it is used for screening the genome for disease diagnosis and thereby designing medicine. This has given way to the personalized healthcare which was otherwise impossible through traditional healthcare system. Extensive study by many research groups have led to the discovery of new genomics based biomarkers for neurological disorders.

Common genomics based techniques used for biomarker study in neurological disorders are discussed.

# Emerging Therapeutic Approaches for Neurodegenerative Diseases

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**Abstract:** The most common neurodegenerative diseases (ND) include Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), as well as frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Protein misfolding and aggregation are the key hallmarks of these neurodegenerative diseases, which may lead to cell death, axonal regeneration failure, demyelination, and overall neuronal structural and functional deficits. Usually, ND is diagnosed at a very advanced stage and conventional therapies are directed at treating neurological symptoms but have no effect on disease progression. In general, several pathological processes contributes to misfolding proteins/protein aggregates and their post-consequences, including impairment of autophagy, microtubule destabilization, neuroinflammation, proteostasis, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, calcium homeostasis, and neurogenesis impairment. Indeed, several signaling pathways critically linked with these pathological processes are now becoming attractive targets and investigated for their beneficial effects by restricting the progression of ND. In particular, certain signaling mechanisms and proteins found to show an integral involvement in the pathogenesis of ND and had shown promising results in preclinical and/or clinical contexts. For ex; novel autophagy stimulators, drugs acting on mTOR, NRF2, TLR, purinergic signaling; drugs acting on neuroinflammatory signaling pathways, Heat Shock Proteins (HSP), sestrins, sirtuins, some PDE-inhibitors, miRNA's have gained a lot of attention in the therapy of ND and are included in the following discussion.

**Keywords:** Heat shock proteins, Neurodegenerative disorder, Neuroinflammation, Novel therapy, miRNA, mTOR, NRF2, PDE inhibitor, Protein misfolding, Purinergic, Sirtuins, TLR.

## INTRODUCTION

Neurodegenerative diseases affect different regions of the brain, but overall they share similar etiology at the cellular and molecular levels. The common feature of

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ND is the accumulation of aggregated proteins as amyloid deposits in different areas of the nervous system. Therefore, ND also called as "Tauopathies", in which, the neurons accumulate abnormal forms of tau, including hyperphosphorylated, conformationally altered, mislocalized, fragmented, oligomeric, and fibrillar forms *i.e.*, amyloid in AD, misfolded Huntington protein in HD, aggregation of ubiquitinated proteins in ALS, Tau and β-amyloid accumulation in MS, α-synuclein accumulation in PD, and tau neurofibrillary tangles in traumatic brain injuries. Conventional therapies for ND, for example, l-dopa for PD and cholinesterase inhibitors for AD, although are used for treatment of the neurological symptoms, substantially do not affect the disease progression. Delayed stimulation of the downstream signaling pathways and regulation of the aberrant genes affect the therapeutic actions of conventional therapy. These signaling pathways and genes promote to multiple pathophysiological processes, including abnormal pro/anti-apoptotic signaling, mitochondrial dysfunction, dysregulation of autophagy, activation of the necrosome by stress and/or inflammation, *etc.*, causing to neuronal degeneration. Recent investigations have been directed toward the characterization of the downstream signaling for treatment, with the promise of identifying novel therapeutic targets. Several signaling pathways and targets have been identified and some of them best characterized are discussed here. Among the signaling mechanisms, mammalian target of rapamycin (mTOR) pathway received high attention, since, it contributes to several pathological aspects of neurodegeneration including autophagy. Moreover, rapamycin and its analogues have shown promising results in the preclinical and clinical trials of ND. Sestrins, a family of evolutionarily conserved stress-inducible proteins, are actively regulated by DNA damage, hypoxia, and oxidative stress. Especially sestrin2, can counteract oxidative stress, reduce mTOR expression, and promote cell survival. Similarly, several autophagy stimulators have been investigated with significant potential in ND. The heat shock proteins (HSP) play a vital role in regulating protein-degradation pathways to repair protein folding by chaperones. Similarly, much work is awaited on drugs acting on macroautophagy. Macroautophagy help to remove misfolded and abnormally aggregated proteins to maintain neuronal health. Sequestosome 1 (SQSTM1/p62) is a scaffold protein closely involved in the macroautophagy process and has shown interaction with the development of ND. Furthermore, SQSTM1/p62 also serves as a signaling hub for multiple pathways associated with neurodegeneration, providing a potential therapeutic target in the treatment of ND. On the other hand, Toll-like receptors (TLR) are well-characterized family of pattern recognition receptors (PRR). The contribution of microglial TLR signaling has been extensively investigated in ND. TLR also plays a significant role in neurogenesis and neurite outgrowth. Further, nuclear factor erythroid 2-related factor 2 (NRF2), a strong regulator of antioxidant response is currently

emerging as a major component of the transduction machinery to maintain proteostasis, critically involved in ND.

Sirtuins (SIRT1-SIRT7) are unique histone deacetylases that interact with multiple signaling proteins, transcription factors and poly (ADP-ribose) polymerases (PARPs) another class of $NAD^+$-dependent post-translational protein modifiers and are considered as a highly promising target in ND. Further, drugs interfering with microtubule (MT) dynamics including MT stabilizers, such as epothilones and taxanes, used for the treatment of cancer have also shown therapeutic effects in ND. Neuroinflammation regulated by resident glial cell microglia is an important pathological marker contributing to disease progression. Leukotrienes are lipid mediators of neuroinflammation. Leukotriene signaling acts in proinflammation stage on microglia and astrocytes. Several molecules acting on the leukotrienes are also investigated in ND. In recent years, the 5-Lipoxygenase (5LO), has gained attention as a therapeutic target in ND. 5LO is a source of inflammatory leukotrienes and is upregulated in AD and related tauopathies. Similarly, microglial NADPH oxidase 2 (NOX2) activation is identified as an important downstream effector of Mac1 signaling involved in the release of proinflammatory factors. Leucine-rich repeat kinase 2 (LRRK2) is a common gene implicated in PD and many inflammatory processes. In addition, researchers have also extensively investigated the role of purinergic signaling in ND. Similarly, phosphodiesterase type 5 inhibitors (PDE5-I) have recently emerged as a potential therapeutic strategy for ND by increasing the expression of nitric oxide synthases and accumulation of cyclic guanosine monophosphate and activating protein kinase G. Thus, the identification of molecules or peptides that interfere with these signaling pathways may prevent the neurodegenerative progression. Some investigations on signaling pathways are promising and can be considered as novel therapeutic approaches in ND.

## mTOR Signaling

The mammalian target of rapamycin (mTOR) is a 289-kD serine/threonine multidomain protein with a kinase domain and an FKBP12 binding domain. mTOR in conjugation with other proteins makes two complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Both complexes located in cytoplasm are phosphorylated by AKT dependent phosphoinositide 3-kinases (Pi3K). mTOR signaling is regulated by insulin, IGF-1, LKB1/AMPK, PI3K/Akt, GSK-3β, IKKβ, MAPK, and p53. Activated mTORC1 may lead to translation of mRNA, suppression of autophagy, ribosome biogenesis, and activation of transcription. Treatment of L-DOPA found to activate mTORC1 involved in neural synaptic rehabilitation in mouse models of PD [1]. The role of mTOR is much explored in AD. In clinical settings, mTOR signaling is found to be closely

# Medicinal Plants and Natural Compounds as Antiparkinsonian Agents

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**Abstract:** Medicinal plants have been used since ages for the treatment of human diseases in the Indian medicinal system of Ayurveda. Parkinson's diseases (PD) on the other hand is a kind of neurodegenerative disorder that shows debilitating symptoms; and the treatment of the disease rely on the symptomatic management. The drugs available for the treatment of the disease show severe side effects on prolonged usage. Thus, many medicinal plants and their derivative natural compounds have been tested for their anti-Parkinsonian activity with minimal side effects. *Mucuna pruriens, Withania somnifera, Tinospora cordifolia* are the example of medicinal plants that have shown anti-Parkinsonian activity while the natural compounds found in medicinal plants like Baicalein, curcumin, Ginseng, Resveratol have also maintained the nerve cell function and prevented the neuronal death. Thus, the polyphenols and other bioactive constituent of medicinal plants should be further studied for their therapeutic intervention against PD.

**Keywords:** Parkinson's disease, Medicinal plants, polyphenols, neurodegeneration, neuroinflammation, oxidative stress, dopaminergic neurons, substantia nigra.

## INTRODUCTION

The selective loss of dopaminergic neurons in the substantia nigra (SN) and resultantly the reduced level of dopamine (DA) in the striatum; is attributed to be the main cause of Parkinson's disease (PD). The reduced level of DA in striatum leads to the imbalance in the level of neurotransmitters like that of DA and acetylcholine. PD patients show symptoms such as tremor, bradykinesia, myoto-

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nia and others that affect their quality of life [1, 2]. The therapeutic strategies followed for the treatment of PD these days depend on relieving the motor symptoms, novel non-dopaminergic drug discovery and development of neuroprotective drugs for modifying the pathogenesis of PD [3]. The etiology of PD is not yet fully understood, but different studies have suggested the role of oxidative stress, neuoinflammation, protein aggregation, excitotoxicity and mitochondrial dysfunction in the pathogenesis of PD [4, 5]. Though, the neuropathological features of PD cannot be wholly mimicked by any known model [6], still the neurotoxin models of PD has stood up as the worthy tool for assessing the adverse effects of PD and developing the novel therapeutic targets [7]. PD has been documented in different parts of the world since ages; and countries of Asia such as India, Japan, China and Korea have been using the herbal based medicines in different combinations based on their experiences [8]. The use of medicinal plants in the treatment of PD attributes to our dependence on products based on natural origin and these plants serve as an important source for the medicines [9 - 15]. Last decade has put an enormous addition in PD research and bioactive constituents in the medicinal plants have been identified that exhibits health-promoting qualities for the treatment of this disease [16]. In China about 22,500 medicinal herbs are used in relevance to PD treatment, but their investigation in experimental models and clinical trials are not yet done to portray them as a potential drug for the disease [17]. Comparatively, many medicinal plants don't have a nutritional role in human diet and are only responsible for managing specific diseases for shorter or longer duration [18]. Therefore, these therapies do need a proper re-investigation of these medications and therapies in pre-clinical studies so as the development of novel therapeutic target can be done [19]. Research in the field of understanding PD is done widely, still there is a need to develop a potential drug candidate for the disease as the available treatment strategies does not meet to the satisfactory results.Apart from only targeting the treatment, neuroprotection should also be taken into consideration so as to inhibit the progression of the disease pathogenesis [20, 21]. Thus, credibility in the treatment strategies can be added by incorporating the bioactive components obtained from the natural origin for the disease management [22]. Exclusively, plant extracts and their derivative; bioactive components has been tested in research laboratories and they have been seen to have great potential to offer neuroprotection and hence stand as a possible drug candidate for PD.The alternative traditional medicine system of Ayurveda is used in India from ancient times and PD is described as "Kampavata" in it [23]. In this medicine system, *Mucuna pruriens* (Mp) has wide importance and is used as a medicine for PD treatment. Furthermore, scientific investigations have reported the presence of levodopa (L-DOPA) that provides long-term prevention from the debilitating symptoms of the disease [23]. Powdered seed formulation of Mp has shown

beneficial effects on PD patients in clinical trials; without showing the associated dyskinesia symptoms. Commercial preparation of Mp, namely Zandopa (HP-200) is available for the treatment of the disease [24].

The pharmacological research deals with the involvement of medicinal plants and their derivatives in targeting the specific sites that result in either neuroprotection or inhibition of the mediators involved in the pathogenesis of PD. The compounds can be enriched with the antioxidant properties in the brain tissue or they can have anti-inflammatory properties that targets neuroinflammation inside the brain. They can also show their effect on the dopaminergic system, either by acting bas an agonist or by reducing the dopamine metabolism. Another group can act as antagonist for muscarinic or ionotropic glutamate receptors in CNS. The best group can act on adenosine receptor as an antagonist; because the relationship between PD and adenosine system has been seen. These all parameters can be an effective target for managing the symptoms of PD and providing better therapeutic strategies [25]. Natural compounds isolated from medicinal plants are being used for treating different neurodegenerative disorders. These plants can be useful in maintaining the nerve cell function and decelerate the loss of dopaminergic neurons in the case of PD. The plants such as *Mucuna pruriens*, *Bacopa monnieri, Withania somnifera, Centella asiatica, Panax ginseng, Pueraria lobata, Paeonia alba, Curcuma longa, and Scutellaria baicalensis* and (Table **1**) have been studied for anti-Parkinsonian activity.

**Table 1. Anti-Parkinsonian activity of Medicinal plants in PD models (adapted from [25]).**

| Medicinal Plants | Family | Experimental Model | Reference |
|---|---|---|---|
| *Solanum lycopersicum* L. | Solanaceae | Rotenone-intoxicated mouse model | [81] |
| *Albizia adianthifolia* W.Wight | Leguminosae | 6-OHDA rodent model | [82] |
| *Centella asiatica* (L.) Urb. | Apiaceae | Aggregation model of α-synuclein | [83] |
| *Crocus sativus* L. | Iridaceae | MPTP-intoxicated mouse model | [84] |
| *Decalepis hamiltonii* Wight & Arn. | Asclepiadaceae | Transgenic *Drosophila* model | [85] |
| *Lycium chinense* Mill. | Solanaceae | Rotenone-induced PC12 cells | [86] |
| *Tinospora cordifolia* | Menispermaceae | 6-OHDA | [87] |
| *Withania somnifera* (L.) Dunal | Solanaceae | MPTP rat model | [88] |
| *Ocimum sanctum* L. | Lamiaceae | *Drosophila* model | [89] |
| *Sida cordifolia* | Malvaceae | Rotenone-intoxicated model | [90] |

# Neuropharmacology in Alzheimer and Huntington Disease

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**Abstract:** The Alzheimer's disease and Huntington's disease are the two important neurodegenerative disorders currently under research for various therapeutic approaches ranging from newer biochemical molecules, plant extracts and food supplements to highly advanced biotechnological and genetic therapies.

Alzheimer's disease (AD), one of the leading causes of disability in the elderly population is exponentially rising worldwide. The acetylcholinesterase inhibitors and memantine, the mainstay of treatment only slow down the disease progression and provide symptomatic improvement. The cholinesterase inhibitors, rivastigmine and donepezil apart from improving cognition also delay hospitalization and reduce behavioural and psychological symptoms of dementia. Other cholinesterase inhibitors and cholinomimetic targets like muscarinic and nicotinic receptor agonists are in development. Extensive research in this area in the past few decades has given insight into the cellular and molecular pathogenesis of the disease. This has led to the development of certain novel strategies to modify the disease progression and prognosis. This includes amyloid and tau-based therapeutics, various immunotherapies, vaccines and food and plant supplements. Other new promising agents under research are anti-inflammatory drugs, neurotrophic factors and antioxidants. Huntington's disease is a rare inherited neurodegenerative disorder producing motor, cognitive and psychiatric symptoms. A greater understanding of the pathology in the recent past has led to research into the development of newer therapeutic agents mainly DNA and RNA based therapies and technologies using gene editing tools.

Several of these putative drugs are in preclinical studies and many of them have failed to show positive results. In this section, we are going to discuss the approved therapies for AD and HD currently in use, the status and evidence regarding drugs in various stages of clinical trial and mention advanced biotechnological and gene therapies under investigation.

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## INTRODUCTION

Dementia is a chronic and progressive condition manifesting as loss of cognitive functions that is age inappropriate and not explained by the natural aging process (WHO). The cognitive functions include memory, attention and concentration, orientation, learning capacity, language, comprehension, calculation and judgement. The most common is Alzheimer's dementia (AD) followed by vascular dementia, mixed dementia and other neurodegenerative disorders like Lewy body disease and Frontotemporal Dementia [1, 2]. Epidemiology, Aetiology, Molecular biology, Pathophysiology and Biomarkers of AD and HD have already been covered in the previous chapters.

## ALZHEIMERS DISEASE

As the life expectancy is continuously increasing, it has led to an increase in the number of patients with dementia, particularly AD. It is expected that people suffering from dementia will rise to 82 million in 2030 and 152 million in 2050. This has led to increased research in the area of new drugs for primary, secondary or tertiary prevention of dementia [1].

Most AD patients come under the category of Sporadic AD, which is further divided into early onset with age less than 65 years (3-5%) and late-onset forms with age more than 65 years (95-97%). The dementia patients having an early onset, around fourth decade are categorised as Familial AD (FAD) and caused by inherited mutations, amounting to 2 percent of the diagnosis [3, 4]. Pathology underlying FAD involves mutations in genes on chromosome 21, chromosome 14 and chromosome 1, coding for amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2), respectively [5, 6]. This results in the formation of beta-amyloid (Aβ), especially the peptide long form (Aβ1-42). Whereas in sporadic AD, approximately 25% patients are carriers of a mutation on chromosome 19 coding for lipid transport protein e4 allele of the ApoE gene (apolipoprotein E). At present, the fundamental mechanisms by which ApoE helps to increase Aβ levels are unclear [3, 7, 8].

As of now, the mainstay of treatment for mild to moderate AD is cholinesterase inhibitors (CIs) which counterbalances neurotransmitter dysfunction underlying the disease. Five medications for the treatment of Alzheimer's disease have been approved by the US Food and Drug Administration (FDA) that provide moderate benefits in memory, behaviour and function. Four of these drugs Psychiatric drugs act by inhibiting acetyl cholinesterase and the fifth drug acts as an antagonist on

N-methyl-D-aspartate receptor (NMDA). Lower dosages of psychiatric medicines like antipsychotics, anxiolytics and antidepressants can be used for the Behavioural and Psychological Symptoms of Dementia (BPSD). Various other treatments under research include compounds targeting extracellular amyloid β (Aβ) plaques and intracellular neurofibrillary tangles, the two major pathological substrates of the disease. Over the past 10 years, many medications have been researched aiming to modify or change the course of the disease [5].

The naturalistic course of AD is one of gradual worsening. Besides, symptomatic management of dementia only slows the progression of the disease while when disease modifying medication is given, further deterioration can be prevented, thereby altering and slowing the path. Treatment is directed towards managing cognitive and behavioural and psychological symptoms, aggression, hostility and insomnia, thereby improving the global functioning of the patient.

## NEUROPATHOLOGY OF AD

Detailed understanding of pathology and neurobiology of dementia is needed to plan treatment for the disease. The main neurotransmitter system involved in AD is the cholinergic neurons predominantly in the basal forebrain. These cholinergic neurons maintain cerebral blood flow in the cortex thereby responsible for cognitive functions like memory, attention, concentration, learning, cerebral cortex growth and sleep wake cycle regulation. Thus, multiple neurobiological involvement of cholinergic system can be partly seen as responsible for symptom complexity and presentation of dementia as a syndrome. Dysfunction in the cholinergic system in AD can be seen at various steps, including decreased activity of enzyme choline acetyltransferase, decreased absorption of choline, decreased acetylcholine synthesis and altered levels of receptors for acetylcholine. Glutamate, another neurotransmitter responsible for proper cortical functioning and cognitive functions, is an excitatory neurotransmitter primarily in the neocortical and hippocampal region of the brain. Glutamate acts on NMDA receptors present on post-synaptic membrane and its excessive secretion in the synaptic cleft due to more presynaptic release and reduced reuptake leads to tonic sustained activation of NMDA receptors.There is excess glutamate present in the extracellular space in AD [9, 10]. This slow and sustained tonic activation or 'excitotoxicity' in AD is in contrast to the acute and short lasting tonic activation seen in stroke and epilepsy. However, in the presence of underlying impaired insulin sensitivity as seen in Diabetes Mellitus, abnormal receptor density and mitochondrial functioning, the normal physiological level of glutamate becomes excito-toxic.

# Brief Description of Public Health and Burden of Neurodegenerative Diseases

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**Abstract:** Physical and mental well-being is treasure for mankind in a competitive and progressive global scenario. For a country, result oriented tasks can be accomplished only with its healthy population. Along with many diseases of global concern, neurological disorders have drawn concern globally as these are sharing an increasing proportion in global burden of diseases. Further cases of neurodegenerative disorders, majorly affecting aged population, have been recently reported to record a considerable increase which has complicated the health and care-giving (old age homes) services as part of public health. Many public health policies have been laid down by many developed and developing countries in accordance of WHO guidelines which in turn based on GBD studies, made till date. Major share of neurodegenerative disorders is contributed by Alzheimer's Disease, Parkinson's Disease, Amyotrophic Lateral Sclerosis & Multiple Sclerosis. The recent past has witnessed growing number of deaths and disability adjusted life years, DALY, caused by neurodegenerative diseases. Public health services and related government policies are not enough, according to WHO, to properly address the current situation. Lack of public awareness towards neurological disorders of all kind, is one of the major challenges to Figure out actual data; for prevalence of neuro-disorders.

**Keywords:** GBD study, WHO, Public health, neurological disorders, Neurodegenerative diseases, Alzheimer's disease, Indian status.

## INTRODUCTION

Health of an individual depends on accessibility of drinkable water, breathable air, hygienic living, proper nutrient supply with adequate meals as per nature of work, work hours, hours of quality sleep and many more. As we can think that, as a set, these all parameters are part of surrounding and environment around an individual, hence their accessibility is not confined only to any one person but to

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the whole community sharing the same surrounding and environment. A demographic distribution has always been impactful, over the sincere and evenly distribution of resources among the respective population; therefore, we count on 'public health' in order to consider health of each individual in a village, town, city or a country. Further being a component of social structure, social well-being is also an important component of psychological-well-being and ultimately of mental health. Public health is major concern for a country to accomplish sustainable development of the country at each front because health of its citizen affect productivity in all aspects and ultimately economy of the country. Providing basic health services is therefore one of the government's primary responsibilities worldwide which include vaccination, self-hygiene awareness, preventing use of drugs of abuse, even promoting small family structure to optimize the availability of resources for each member of the family. We can sum up public health as a multidisciplinary field with aim of propagating knowledge and practices to prevent spread of communicable and non-communicable diseases. World Health Organization (WHO) has key role in setting up policies for health services in countries worldwide through its program 'WHO Special Initiative for Mental Health (2019-2023): Universal Health Coverage for Mental Health', launched in 2019 [1] and followed-up program successively [2]. Major non communicable diseases (NCD) that are central to public health goals include cancer, cardiovascular, diabetes, respiratory and communicable infectious diseases [3]. (Fig. **1**) presents an overview for major diseases of global concern, based on number of deaths caused by these diseases individually. Stroke, (classified as neurological disorder under International Classification of Disease, ICD-11) is second in the list of top ten cause of global deaths [4]. This list also includes Alzheimer's disease and other Dementia at seventh place as cause of global deaths. Together these two neurological disorders (NDs) claimed approximately six million deaths globally in 2020, according to WHO [5]. Recent studies have come up with data that shows a considerable, alongside to above mentioned diseases, an increase in cases of neurological disorders all over the world; where developed countries are found to have comparatively a large case registry against developing countries and also against their own history. An unhealthy individual is naturally become a burden for himself/herself and his family, so for the society. Likewise unhealthy population is burden to a society and its country that needs to be addressed on an urgent basis by the country itself and in collaboration with other countries in case of diseases affecting global population. For example, recent pandemic of COVID 19, its global impact and persistence over time has bring about vigorous changes in health programs worldwide [6], as it has affected all aspects of growth of all nations, from academics to economy to families in isolation, as well as, an entity in society.

Global deaths and top 10 cause
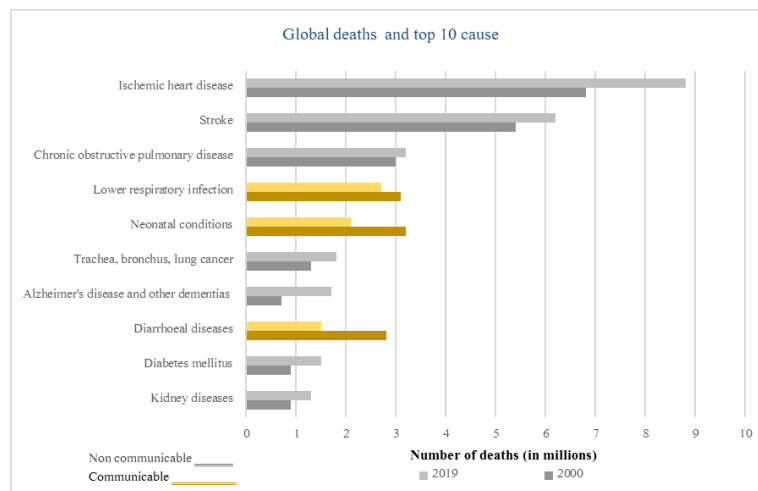
**Fig. (1).** A graphical summary for top ten diseases which are leading cause of deaths globally. (Source: WHO global health estimate).

## STAKEHOLDERS IN PUBLIC HEALTH

Awareness is key to achieve health goals both at individual level and at public level. The role of government is primary which is supported by a well-informed population that provide health care services through NGOs, societies, organizations in public and private set-ups. World Health Organization, is the supreme body at international level that guide and monitor health policies and their implementation at global scale. Under leadership of WHO, some global health projects and programs are running in public private partnership [1, 6], and in India the 'National Health Mission (NHM)' is being run by Government of India targeting urban (NUHM) and rural (NRHM) population [7].

Towards public health goal, developed countries move a huge fund towards health sector as compared to developing countries. According to Economic Survey, 2019-20, India - a developing country, has health expenditure budget of 1.6% of GDP as compared to that of Germany (9.4%), USA (8.5%) and China (3.2%) [8]. Public health policies of a country are concerned with, majorly, prevention of diseases, creating an 'accessible and affordable to all' health services infrastructure and these all-together aim to increase life expectancy along with health, so the productivity of a country.

'GBD – Global Burden of Diseases' is a study being carried out periodically as international project by WHO in collaboration with world bank and the Harvard School of Public Health [9]. Recent GBD study have estimated some diseases which are leading cause of death globally. The data provided by WHO shows that while there is a global success to control many diseases during a period from year

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