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Ghulam Md Ashraf *Editors*

Mechanism and Genetic Susceptibility of Neurological Disorders

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This book is dedicated to my mother
(Anisun Nisa) whom we lost in 2021

Preface

Neurological disorders comprise a diverse array of medical conditions that impact the nervous system, encompassing the brain, spinal cord, and peripheral nerves. These disorders give rise to a wide spectrum of symptoms and impairments, and their origins stem from a variety of factors, including genetic predisposition, infections, autoimmune reactions, and environmental influences. Risk factors for neurological disorders are multifaceted and depend on the specific disorder in question. Nonetheless, certain general risk factors may heighten the likelihood of developing neurological conditions. These encompass age, genetic elements, environmental exposures, infections, autoimmune disorders, lifestyle factors, trauma, chronic health conditions, and psychological factors. It is important to note that not everyone with these risk factors will develop a neurological disorder, as many neurological conditions are intricate and result from multiple factors. Moreover, ongoing research continues to unveil fresh insights into the risk factors and causes of various neurological disorders, leading to advancements in prevention and treatment. Timely identification and management of these risk factors, in conjunction with a healthy lifestyle, can help mitigate the likelihood of developing neurological disorders in some cases. At present, there is no definitive cure for numerous neurological disorders, but existing therapeutic approaches can provide symptomatic relief and enhance the quality of life for patients. Today, there is a global endeavor to combat the development and progression of neurological disorders. The book titled *Mechanism and Genetic Susceptibility of Neurological Disorders* delves into emerging evidence regarding the genetic underpinnings of neurological disorders and their contributions to disease onset and pathology progression. This book contains a wealth of specific research updates.

Esteemed researchers and scientists from around the world contribute to a thorough understanding of neurological disorders and their mechanisms. The following chapters offer an in-depth exploration of neurological disorders, shedding light on the genetic factors and molecular mechanisms involved in disease progression. The chapters within this book illuminate the mechanistic aspects of various genetic markers in the pathology of neurological disorders, emphasizing how mutations in these genetic markers drive disease progression. Additionally, the book highlights the advanced molecular techniques employed by the scientific community to investigate the multifaceted factors involved in the progression of these disorders. The compilation *Mechanism and Genetic Susceptibility of Neurological Disorders* is the

most comprehensive and exhaustive work of its kind. This comprehensive compilation provides a thorough exploration of the current state of research in the field of neurological disorders and their corresponding treatment options. The editors have skillfully laid a strong groundwork for this topic, addressing the requirements of scholars and medical practitioners alike. This book serves as an invaluable resource for academics, scientists, educators, and students seeking to enhance their knowledge in this domain.

Chapter 1 discusses the neuropathology, the key pathological characteristics, genetic mutations, and pathological changes associated with various neurological disorders, offering a comprehensive understanding of their underlying mechanisms.

Chapter 2 provides a comprehensive overview of head trauma, including its causes, the physiological changes it induces in the brain, the observable clinical symptoms, and the potential biomarkers associated with it.

Chapter 3 presents the comprehension of how DNA methylation contributes to the development and progression of neuropathic pain.

Chapter 4 explores the process of deciphering mutations in the dystrophin gene, aiming to uncover the underlying complexities of muscular dystrophy.

Chapter 5 provides valuable insights into understanding the causes of ataxia and its underlying mechanisms, with a focus on autoimmune, toxicological, and genetic perspectives.

Chapter 6 focuses on the aberrant regulation of miRNA (microRNA) in the context of schizophrenia, aiming to shed light on its role in the disorder.

Chapter 7 discusses the fundamental cellular and molecular mechanisms involved in muscular dystrophy while exploring a range of nanotherapeutic strategies for its treatment.

Chapter 8 examines the processes of axonal degeneration, disrupted axonal transport, and synaptic dysfunction in motor neuron disorders, providing insight into their roles in the disease.

Chapter 9 explores changes in receptor genes as they relate to Huntington's disease, offering insights into their potential implications in the disorder.

Chapter 10 investigates genetic modulators and their role in the context of Amyotrophic Lateral Sclerosis (ALS), providing insights into how genetic factors influence the disease.

Chapter 11 discusses modulators and their impact on behavioral changes that occur after a stroke, shedding light on factors influencing post-stroke behavior.

Chapter 12 explores presynaptic dysfunction as a key aspect of Parkinson's disease, offering insights into how it contributes to the disorder's pathophysiology.

Chapter 13 highlights the involvement of mitochondrial dysfunction in various neurological disorders, highlighting its significance in their development and progression.

Chapter 14 investigates the intricate molecular and cellular mechanisms through which pathogens invade the central nervous system, focusing on the specific case of meningitis.

Chapter 15 addresses the topic of muscular dystrophy with a specific focus on mutations occurring in the dystrophin gene.

Chapter 16 investigates the application of gene editing tools for the treatment and management of neurodegenerative diseases, providing insights into their potential therapeutic benefits.

Chapter 17 provides a comprehensive overview of lumbar disc disease, offering insights into its causes, symptoms, and management.

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Kindness is much more than deeds. It is an attitude, an expression, a look, or even a gentle touch. It is anything that lifts another person. In this little space, we try to acknowledge the support and inspiration of all the people who have been a part of our lives and have contributed knowingly or unknowingly in successful completion of this book.

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About the Editors

Andleeb Khan is an Associate Professor in Integral University, Lucknow, India. She has completed her doctorate from Jamia Hamdard, New Delhi, India in Toxicology with specialization in natural and active constituents from plants for prevention of Alzheimer's Disease. She has joined as Faculty at Jazan University, Saudi Arabia. She has a teaching and research experience of more than 10 years in neurodegenerative disorders and their prevention with medicinal plants, their active principles and nanoformulations. Her accomplishment at academics in Master course is outstanding and was able to get the gold medal, the highest accomplishment for the topper of this course. She has published more than 100 of research publication in national and international journals and contributed many book chapters with international publishers. Dr. Khan is on the editorial board panel and reviewer of various international journals. Dr. Khan is handling many projects of national and international importance. She has received many awards, appreciations, and recognitions for her services to the science. She holds life memberships of various international organizations and is active participant in national and international scientific events. Currently, Dr. Khan is engaged in studying the molecular mechanism of Alzheimer's disease, Ischemic stroke, Parkinson's Disease and their prevention by various active principles from natural sources and nanoformulations.

Mashoque Ahmad Rather is a highly accomplished Postdoctoral Research Associate in the Department of Molecular Pharmacology and Physiology at the College of Medicine, University of South Florida, United States. His academic journey and research career have been distinguished by a deep commitment to understanding the critical neuroscientific aspects, particularly in the context of Alzheimer's Disease. Dr. Rather's educational background includes a doctorate in Biotechnology, with a specialization in neuroscience, which he earned from Annamalai University in Tamil Nadu, India. His rigorous training and expertise in the field of neuroscience have served as a solid foundation for his subsequent research endeavors.With over 8 years of dedicated research experience, Dr. Rather has made significant contributions to the scientific community. He has an impressive track record of authoring numerous research papers published in reputable international journals. Additionally, his expertise extends to the creation of insightful book chapters that have further

enriched the scientific literature. Dr. Rather is a reviewer of various international journals. At present, Dr. Rather is deeply immersed in an exciting and vital area of research. He is actively engaged in investigating the molecular mechanisms underlying Tau pathology and cerebral vascular dysfunction in Alzheimer's Disease. His work in this field holds great promise for shedding light on the complex biological processes involved in Alzheimer's Disease, potentially leading to valuable insights for the development of future therapeutic interventions.

Ghulam Md Ashraf is working as an Associate Professor in the Department of Medical Laboratory Sciences, College of Health Sciences, and Sharjah Institute for Medical Research, University of Sharjah, Sharjah, United Arab Emirates. He has a PhD degree in Biochemistry with over 12 years of teaching and research experience in various disciplines of biological and medical sciences. Dr. Ashraf has taught various subjects like Biochemistry, Biology, Clinical Biochemistry, Cell Biology, Genetics, Immunology, Intellectual Property Rights, Introduction to Research, Molecular Biology, Neurology, Recombinant DNA, and Research Methods Technology at graduate and post-graduate levels.His primary fields of research are biochemistry and neurology, currently focusing on understanding the molecular and behavioral mechanism of effects of anti-diabetic drugs in psychotic and dementia conditions. Dr. Ashraf's lab is currently investigating the effect of anti-diabetic drugs in the possible attenuation/reversal of anti-psychotic drugs induced weight gain in psychotic conditions. He is also investigating molecular and behavioral mechanisms of novel therapeutic combinations in multiple sclerosis and Alzheimer's disease. Dr. Ashraf has published 398 research articles (citations: 10289, H-index: 53, i10 index: 210) and have been involved in 25 research grants [4 ongoing (1 PI, 3 CoI) and 21 completed (17 PI, 4 CoI)]. He has supervised 3 PhD, 2 masters, and 7 bachelor students in their research projects. Dr. Ashraf has served as examiner of 9 PhD and master theses and have assessed 4 research grant applications.Dr. Ashraf is also involved extensively in editorial roles in renowned scientific journals. He has to his credit 397 Publons verified editor records, and 629 Publons verified reviewer records. Dr. Ashraf has been involved as guest editor of 21 special issues in reputed international journals. He is professionally associated with the Royal Society of Medicine (Fellow), Royal Society of Biology (Member), American Society for Biochemistry and Molecular Biology (Member), and Canadian Association of Neuroscience (Member).For his scientific contributions, Dr. Ashraf was approved as a subject of biographical record in Marquis Who's Who in the World (2020). Dr. Ashraf has been recognized as Expertscape World Expert in Alzheimer's disease and Neurodegenerative Disorders. Most recently, he has been listed in Top 2% Scientists Worldwide since 2021.

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Neuropathology of Neurological Disorders

1

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Abstract

Neuropathology delineates the examination of cells and tissues, to assimilate the structure and function of the neurological system as well as the diagnosis and pathology of diseases that impact the nervous system. It studies the effects of disease on the nervous system and can be used to diagnose and categorize particular neurological conditions. This comprises studies of the muscles, nerves, and ganglia (the peripheral nervous system), and the brain and spinal cord (the central nervous system). A wide array of techniques such as immunohistochemistry, molecular biology, and light and electron microscopy are being used to observe neuropathological alterations in various neurological disorders. Neuropathology highlights the structural and functional observations of neurological diseases ranging from cellular to micro-anatomical constructs to identify the biomarkers that are responsible for the progression of the diseases. Several imaging technologies are also used which include CT scans and MRI to deeply

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examine the modifications in neurological disorders. The examination of several neurological disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and multiple sclerosis, rests severely on neuropathology. In this chapter, we will discuss about the neuropathology of several neurological disorders.

Keywords
Neuropathology · Amyloid-β · Tau · Lewy bodies · HTT gene · MS · CVDs

1.1 Introduction

Neurological disorders involve a wide range of conditions that affect the structure and function of the nervous system, resulting in a variety of symptoms and limitations. These disorders can be caused by several factors, such as genetic mutations, infections, environmental influences, autoimmune responses, and degenerative processes. To understand their underlying processes and symptoms, a thorough examination of their neuropathology is crucial venture. Neuropathology looks into the structural and molecular changes that occur in the nervous system as a result of disease or injury. It focuses on the analysis of tissue samples taken from the brain, spinal cord, and nerves through autopsy, surgery, or biopsy. Neuropathologists can identify the precise changes and anomalies linked to various neurological disorders by microscopic examination of the tissue samples. Finding the pathological markers or lesions that characterize particular disorders is one of the core parts of neuropathology. These distinguishing characteristics might manifest in several ways, such as aberrant protein aggregation, neuronal loss, inflammation, demyelination, and vascular abnormalities. These distinguishing characteristics aid in the establishment of diagnostic standards and therapeutic approaches and offer vital insights into disease progression.

To understand the genetic underpinnings of neurological disorders, neuropathology is equally crucial. The identification of several disease-causing genes and the detection of genetic alterations linked to a variety of disorders have been made possible by advancements in molecular techniques. Researchers can identify particular genetic defects that contribute to the onset and progression of neurological diseases by analyzing DNA and RNA extracted from patient samples. Neuropathology also helps us understand how diseases develop and how their symptoms are related to one another clinically. Researchers can clarify the temporal and spatial patterns of pathological alterations by studying the brain and spinal cord tissues at various stages of the disease. This information aids in the creation of tailored treatment approaches, the establishment of disease staging systems, and prognosis prediction. The intricate interactions between distinct cell types in the nervous system are further illuminated by the neuropathology of neurological disorders. In response to disease, several cell groups, such as immune cells, glial cells, and neurons, can experience pathological changes. Understanding the mechanisms driving neuronal malfunction, inflammation, neurodegeneration, and neurorepair is made possible by the study of these biological alterations.

Thus, unraveling the underlying causes of neurological disorders, identifying diagnostic indicators, and creating efficient treatments depend on a thorough understanding of the neuropathology of these conditions. The discipline of neuropathology continues to offer essential insights into the intricate structure of neurological disorders by implementing advanced technical breakthroughs, opening the way for improved diagnosis, treatment, and management of these conditions. The most common neurological disorders include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic lateral sclerosis (ALS), which are usually progressive and may worsen over time. The symptoms of these diseases vary depending on the type, and they can range from mild to severe. Therefore, in this chapter, we will discuss about the neuropathology of several neurological disorders.

1.2 Degenerative Disorders

Degenerative diseases are a group of medical conditions that gradually deteriorate the body's cells and tissues. These diseases are typically chronic and can deteriorate over time. The most prevalent degenerative disorders are AD, PD, and HD. The symptoms of these diseases vary depending on the type, and they can range from mild to severe. Thus, the risk factors, pathological alterations, clinical manifestations, and progression of the diseases have been given in Table 1.1.

1.2.1 Alzheimer's Disease

The most typical cause of dementia is AD, a progressive, neurodegenerative ailment depicted by psychological and behavioral symptoms as well as a slow deterioration of cognitive function. The underlying pathology of AD consists of two irregular protein fragments called Aβ lesions and neurofibrillary tangles (NFTs) in the brain. Amyloid plaques consist of the β-amyloid (Aβ) peptide, which is generated by the cleavage of amyloid precursor protein (APP). Aβ peptides are produced in a variety of lengths, with Aβ42 being the most common and most toxic form. These plaques accumulate in several brain sections, including the neocortex, hippocampus, and amygdala (Liu et al. 2019). The NFTs are comprised of hyperphosphorylated tau, which accumulates in the neurons of the brain (Ahmad et al. 2019; Arafah et al. 2023). Tau proteins are typically found in the axons of neurons, where they help to stabilize microtubules and maintain the proper shape of the cell. In AD, tau proteins become abnormally phosphorylated and aggregate together to form NFTs. These tangles are most commonly found in the hippocampus, amygdala, thalamus, and basal ganglia. Besides NFTs and Aβ lesions, AD is also characterized by oxidative stress, neuroinflammation, and synaptic dysfunction (Rehman et al. 2023). Astrocytes, activated microglia, and pro-inflammatory cytokines are all indicators of neuroinflammation in the brain (Rather et al. 2021). Oxidative stress is brought on by an excess of reactive oxygen species (ROS), which can harm cellular

Table 1.1 An overview of risk factors, pathological and functional alterations, clinical presentations, and diagnosis in different neurological disorders

Disorders	Risk factors	Pathological alterations	Functional alterations	Clinical presentation	Disease progression	Diagnosis	References
AD	Genetic predisposition, environmental factors, infections, trauma, toxic substances	Abnormal protein accumulation of Aβ and Tau, neuroinflammation, oxidative stress, synaptic loss, and neuronal death	Impaired neuronal signaling, altered neurotransmitter release, disrupted neuronal circuits, sensory disturbances, and cognitive decline	Memory loss, language difficulties, vision loss, mood swings, and personality changes	Further accumulation of pathological changes, increased functional impairment, and potential involvement of additional brain regions	Clinical assessment (history, physical examination), neuroimaging, biomarker analysis (CSF, blood tests), and neurophysiological testing	Hardy (2009), Salomone et al. (2012), Roth et al. (2005)
PD	Environmental factors, past traumatic brain injury, exposure to toxic substances, and drugs and medication	Dopaminergic neuronal damage in the basal ganglia, particularly in the substantia nigra, and atypical Lewy body formation from α-synuclein	Motor abnormalities, loss of functional mobility, and stooped posture	Body tremor, muscle rigidity, mood swings, sleep disorder, fatigue, speech and cognitive problems	Dopamine depletion, Lewy body formation, neuroinflammation, oxidative stress, mitochondrial dysfunction, and neurotransmitter imbalance	Medical history, parkinsonian symptoms, and response to levodopa imaging tests	Schulz-Schaeffer (2010), Dexter and Jenner (2013), Tufekci et al. (2012)
HD	Genetic mutation, age, sex, and familial history	Mutation in the HTT gene, production of mutant huntingtin protein, aggregation of abnormal protein, impairment in protein trafficking, calcium homeostasis, and neuronal dysfunction	Disrupted signal transmission, basal ganglia impairment, imbalance of neurotransmitters, cognitive decline, dystonia, bradykinesia, and anxiety	Involuntary movements, cognitive decline, psychiatric disturbances, and various motor and behavioral alterations	Neuroinflammation, excitotoxicity, neurotransmitter impairment, disruption in cellular transport, mitochondrial dysfunction, synaptic loss, neuronal dysfunction, age, and environmental and lifestyle factors	Clinical evaluation, genetic testing, and medical imaging such as MRI and computed tomography	Vonsattel et al. (2008), Gu et al. (2005), Spampanato et al. (2008)

Disorders	Risk factors	Pathological alterations	Functional alterations	Clinical presentation	Disease progression	Diagnosis	References
MS	Genetic and environmental factors, gender, and age	Inflammatory demyelination, lesion formation throughout the CNS, reactive gliosis, and gray matter damage	Motor function impairment, damage to sensory pathways, fatigue, cognitive dysfunction, and bladder and bowel dysfunction	Optic neuritis, fatigue, numbness, depression, and walking difficulties	Autoimmune response, inflammation, axonal damage, demyelination, neuroplasticity, and neurodegeneration	Medical history, neurological examination, CSF analysis, evoked potentials, and imaging analysis	Kornek and Lassmann (2003), Lemus et al. (2018), Ghasemi et al. (2017)

structures and result in cell death. Synaptic dysfunction is due to the loss of synapses in the brain, which is thought to be caused by the accumulation of Aβ plaques and NFTs (Khan et al. 2012a).

The Aβ, tau, and inflammatory assumptions are only a few of the assumptions that have been advanced to explain this complex disorder (Kumar and Dogra 2008). Researchers have highlighted the function of Aβ oligomers in synaptic damage, demonstrating that Aβ oligomers are one of several factors to disfigure the neuronal integrity (Anand et al. 2014; Dal Prà et al. 2014). The amyloid cascade hypothesis postulates that the APP is processed abnormally by β- and γ-secretases after being normally cleaved by α-secretase, resulting in an imbalance in the synthesis and clearance of Aβ peptide (Salomone et al. 2012). As a result, Aβ peptides instinctively aggregate into soluble oligomers, then combine to form insoluble fibrils, which are subsequently accumulated as diffuse senile plaques (Hardy 2009). According to research by Kurz and Perneczky (2011), Aβ42 oligomers cause oxidative damage, encourage hyperphosphorylation of Tau protein, and have a negative impact on synapses and mitochondria.

Proinflammatory cytokines, such as TNF, IL-1β, and IFN-γ, are generated and released when microglial cells are activated. Consecutively, these cytokines activate further Aβ42 production and distribution by encouraging the adjacent astrocyte-neuron to generate more Aβ42 oligomers (Dal Prà et al. 2014). Aβ oligomers are believed to be the cause of the neuronal degeneration in AD brains, which causes oxidative damage and reduces the ability of the neurons to scavenge free radicals (Roth et al. 2005; Galimberti et al. 2013).

The clearance of Aβ oligomers from the brain is primarily mediated by the insulin-degrading enzyme (IDE) and proteases neprilysin-mediated proteolytic degradation, astrocytes, and microglia (Yasojima et al. 2001; Braak and Del Tredici 2011). Increased NO levels have been shown to inhibit IDE's enzymatic activity, which leads to the build-up of Aβ oligomers in the brain and the onset of AD (Tuppo and Arias 2005). According to earlier research, hyperphosphorylated tau oligomers and Aβ42 oligomers diffuse via exocytosis to astrocyte and oligodendrocyte target cells, which then develop into cells that manufacture Aβ and tau oligomers (Eisele et al. 2010).

1.2.1.1 Amyloid Plaques

The amyloid cascade hypothesis was evolved in response to the illustration of Aβ as an essential component of Aβ plaques (Hardy and Selkoe 2002), and genetic affirmation linking the APP protein and its processing by β- and γ-secretases to autosomal dominant AD forms (Goate et al. 1991; Levy-Lahad et al. 1995). Research studies investigated that Aβ deposits diffuse in the brain in a routine style that can be categorized into five distinct phases (Thal et al. 2002). The first phase reveals its early deposition in the neocortex, and, the second, its development is seen in the limbic areas which include amygdala, entorhinal cortex, subiculum, and cingulate gyrus. In the third phase, Aβ accumulates in subcortical areas including the thalamus and basal ganglia, followed by the fourth phase which

affects the midbrain, pons, and medulla oblongata, and then finally it spreads to the cerebral cortex.

There are perceptible amounts of accumulates in the cerebral blood vessels called cerebral amyloid angiopathy (CAA), which is commonly observed in AD patients, in addition to the production of Aβ aggregates in the brain parenchyma (Bergeron et al. 1987; Jellinger et al. 2007). The breakdown of blood artery walls and subsequent risk of cerebral hemorrhages are critical side effects of vascular Aβ deposition (McCarron and Nicoll 1998). Deterioration of this process appears to be a significant contributing element to the onset of sporadic AD (Greenberg et al. 2020). The severity of arterial wall integrity damage and the location of CAA throughout the brain have both been rated using several neuropathological staging approaches to quantify CAA (Vonsattel et al. 1991; Thal et al. 2010). Whichever of these conditions is employed, it is evident that more severe pathology is connected to more intense outcomes, such as micro- or macro-hemorrhage or infarcts (Thal et al. 2010). The biomarkers enable the monitoring of the appearance of Aβ accumulates in AD subjects. Researchers suggested that imaging using Aβ-specific positron emission tomography (PET) ligands could provide a generalized picture of Aβ pathology's regional distribution (Hampel et al. 2021). A reduction of Aβ1–42 or of the ratio of Aβ1–42/Aβ1–40 is a good predictor of Aβ pathology in the brain. To validate that the performance of biomarkers is as accurate as predicted in individuals treated with Aβ altering treatments, comprehensive autopsy studies are still required.

1.2.1.2 Tau

Tau, a protein associated with microtubules, accumulates to form NFTs, the second main pathogenic finding in AD. To find a stereotypical pattern of dissemination of these aggregates, Braak and colleagues used whole hemisphere 100-m-thick sections of 83 brains using silver-staining techniques in a seminal work (Braak and Braak 1991). The hippocampal formation's trans-entorhinal area (stage I) is where the first NFT were discovered. From then, the number of aggregates increases and spreads to the hippocampal pyramidal cell layer's subiculum (stage II). "Trans-entorhinal stages" refers to this early manifestation of NFT pathology (Braak and Braak 1991). NFT begins to affect the hippocampal pyramidal cell layer and entorhinal cortex as the disease progresses, especially sector CA1 (stage III). Sectors CA1–CA4 of the hippocampus pyramidal cell layer and the neighboring inferior temporal cortex are among the regions where the modifications are most pronounced. The superior temporal cortex and frontal cortex are two further neocortical regions where NFT disease has spread (stage IV).

Since the hippocampus formation is most severely impacted, these transitional stages are frequently denoted as "limbic stages." The abnormalities in the hippocampus formation worsen as the disease progresses, but they also impact other parts of the neocortex, such as secondary association areas and finally primary cortical areas. As a result, these advanced illness stages are referred to as "isocortical stages" (Braak and Braak 1991). A segment of the occipital cortex is routinely studied to determine the stages of this progression; stage V is defined by the illness in the

peristriate area, and stage VI is defined by intraneuronal aggregates in the striate area. While stages I and II are frequently found in clinically asymptomatic subjects, Braak stages V and VI have the best correlation with clinically recognized dementia (Braak and Braak 1991).

The development of NFT appears to be caused by tau redistribution from the axonal section to the somatodendritic section and aberrant tau phosphorylation, and studies using antibodies that are specific for phosphorylated tau demonstrated earlier phases of tau aggregation in neurons, presumed pre-tangles (Braak et al. 2011). Additional systematic research was conducted as a result, and some of these purported precursor lesions were observed in the brain's stem's neuronal populations, most notably the locus coeruleus. This broadened our understanding of tau pathogenesis in humans with regard to the anatomical distribution and age range of afflicted individuals (Stratmann et al. 2016; Ehrenberg et al. 2017). The hypothesis that tau appears to migrate across physically related places has inspired major research endeavors to uncover a "prion-like" tau spreading mechanism between connected neuronal populations in animal models and possibly even in human AD patients (Dujardin and Hyman 2019). Although the precise methods by which tau may cross synapses to neighboring neurons are yet unknown, understanding this process may be essential to the creation of disease-modifying treatments. The discovery of initial lesions in the locus coeruleus has also prompted investigations into the origins of pathogenic protein aggregation in enteric neurons and putative linkages to peripheral organs (the "gut-brain axis") (Kowalski and Mulak 2019) (Fig. 1.1).

1.2.2 Parkinson's Disease

PD is a progressive neurodegenerative disease represented by the degeneration of dopaminergic neurons in the substantia nigra of the midbrain. The primary cause of this death is unknown, although it is presumed to be related to genetic, environmental, and/or lifestyle factors. Tremor, stiffness, bradykinesia, and postural instability are just a few of the symptoms that develop as the illness worsens (Reich and Savitt 2019). The pathology of PD involves the degeneration of dopaminergic neurons in the substantia nigra pars compact (SNpc), as well as the presence of intraneuronal inclusions called Lewy bodies (LBs) (Raza et al. 2019; Aryal et al. 2020). These LBs are made up of aggregates of proteins, including α-synuclein, ubiquitin, and neurofilament proteins. The presence of LBs is considered to be the cause of the dopaminergic cell death, as these aggregates are toxic to the neurons (Khan et al. 2012b). Besides the loss of dopaminergic neurons, PD is also associated with other neuropathological changes, including gliosis, inflammation, and the existence of aberrant mitochondria. Gliosis is the replacement of lost neurons by astrocytes and microglia, which can worsen brain inflammation and injury. Pro-inflammatory cytokines are released during inflammation, which can cause neuronal damage and the formation of LBs. Abnormal mitochondria can also contribute to neuronal death, as they are unable to produce sufficient energy for the cell to function properly (Khan et al. 2012b). Overall, PD is a complex disorder that involves an array of different

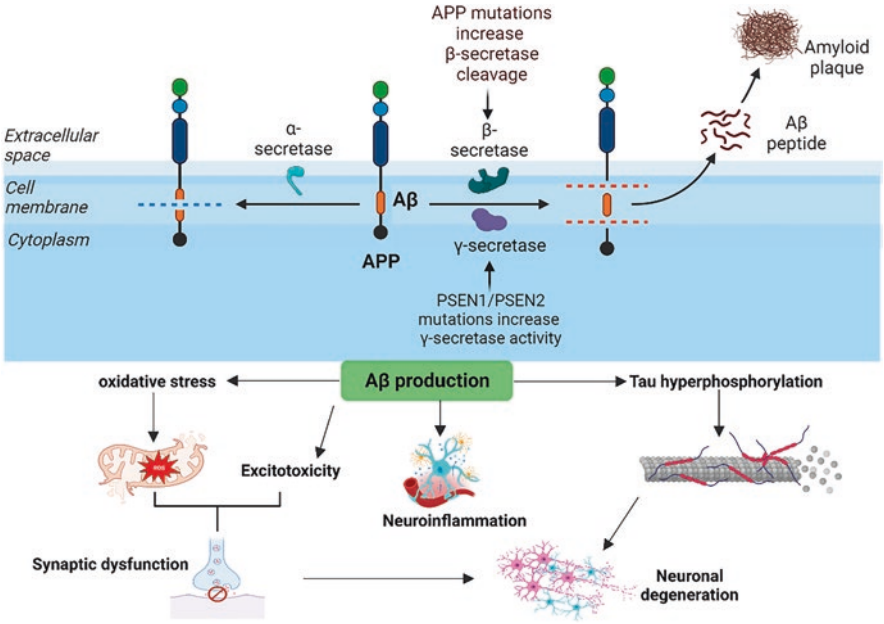

Fig. 1.1 Pathology of AD. The formation of amyloid plaques is associated with the production of Aβ peptides. Alterations in the APP lead to an increased cleavage by β-secretase, contributing to the production of these peptides. Additionally, PSEN1/PSEN2 leads to augmented activity of γ-secretase, further promoting the Aβ peptide production and the development of Aβ lesions. These Aβ lesions subsequently induce hyperphosphorylation of the Tau protein, oxidative stress, excitotoxicity, and disruptions in synaptic function. Therefore, these peptide aggregates stimulate oxidative stress and facilitate inflammatory processes within neurons. This inflammatory response, in turn, amplifies the expression of APP, leading to increased production of Aβ peptides. Hence, this process ultimately culminates in neuronal damage and AD progression

pathological changes. The primary cause of death is the deterioration of dopaminergic neurons in the substantia nigra, along with the occurrence of LBs.

The neuropathology of PD also involves changes in other brain areas, such as the basal forebrain, hippocampus, and amygdala. In the basal forebrain, neurons that produce the neurotransmitter acetylcholine (ACh) begin to die, resulting in a decrease in the amount of ACh available to the brain (Alexander 2004). This can lead to memory and behavioral deficits, as well as disturbances in motor control. The hippocampus is also affected in PD, as it is a major target of the dopaminergic neurons. Neuronal degeneration in the hippocampus can lead to memory impairments and difficulty with learning new information (Llewelyn et al. 2022). The amygdala brain region is involved in the processing of emotions and motivation. Neuronal disintegration in this region has been connected to changes in mood and behavior, as well as an overall decrease in motivation (Khan et al. 2010). Finally, PD is also associated with changes in the cerebellum, which controls balance and coordination. Neuronal loss in this region can lead to an increased risk of falls, as well as difficulty with fine motor control (Wu and Hallett 2013). Overall, the

neuropathology of PD involves a variety of different changes in the brain, all of which can contribute to the progression of the illness. The primary cause of death is still unknown, but various environmental, genetic, and lifestyle factors are believed to play a role.

The LBs and dystrophic neurites within nerve pathways, as well as within the synaptic compartment, are hallmarks of the histopathology of PD. These pathological characteristics are particularly concentrated within the presynaptic terminals across the CNS (Muntane et al. 2008; Schulz-Schaeffer 2010). Numerous subcortical nuclei, particularly the substantia nigra compacta (SNc), locus coeruleus, and dorsal motor nucleus of vagus, as well as many other neuronal systems, are linked to variable neuron loss. The A-9 group of SNc is severely affected by the reduction of melanized and dopaminergic neurons that express tyrosine hydroxylase (TH), an essential substance for dopamine production. This leads to striatal denervation and dopamine decline of 44–98%, which are symptoms of nigrostriatal degeneration (Rajput et al. 2008). As dopamine degenerates, initial disease stages witness a rise in striatal dopaminergic neurons, possibly due to phenotypic shifts rather than neurogenesis (Porritt et al. 2006; Tandé et al. 2006). While MRI studies revealed early striatal volume deviations, similar alterations in the olfactory bulb might imitate a compensatory mechanism (Mundinano et al. 2011) that may be more effective in younger PD subjects (de la Fuente-Fernandez et al. 2011).

In early-onset PD, nigrostriatal dopaminergic neuron loss is greater than in late-onset PD (Shih et al. 2007). The dopamine impairment was discovered by longitudinal PET investigations approximately a decade before the onset of the disease in older PD patients. This impairment might even exist for up to 25 years prior to symptoms in younger subjects. Thus, the period before clinical symptoms varies depending on the age of onset. Prior to the inception of motor symptoms, the dopaminergic system can sustain more damage in younger PD subjects. The final-stage PD patients displayed a dramatic loss of SN neurons along with substantial cell atrophy (Rudow et al. 2008). Recent SPECT investigations, however, showed that even after many years of sickness, the dopaminergic system is not completely degenerated, with the loss being more pronounced in the putamen than in the caudate nucleus (Djaldetti et al. 2011).

Before the degeneration of SN cells, various indicators of functional neuronal damage are already affected. This includes the loss of neurofilament proteins, mRNA, immunoreactivity of neuronal TH and DAT, as well as cyclooxygenase (COX) activity (Kingsbury et al. 1999). The loss of neurons is accompanied by an astroglial response, neuronophagia, and extracellular neuromelanin release that is taken up by macrophages (McGeer and McGeer 2008). In the afflicted nigrostriatal system, there is evidence of microglial activation and associated dopaminergic terminal loss point to the possibility that neuroinflammatory reactions play a role in the ongoing degenerative process (Pradhan and Andreasson 2013; Tufekci et al. 2012). In PD, α-Syn plays a significant part in the development and maintenance of inflammation (Alvarez-Erviti et al. 2011). However, this role appears to shift from being beneficial in the disease

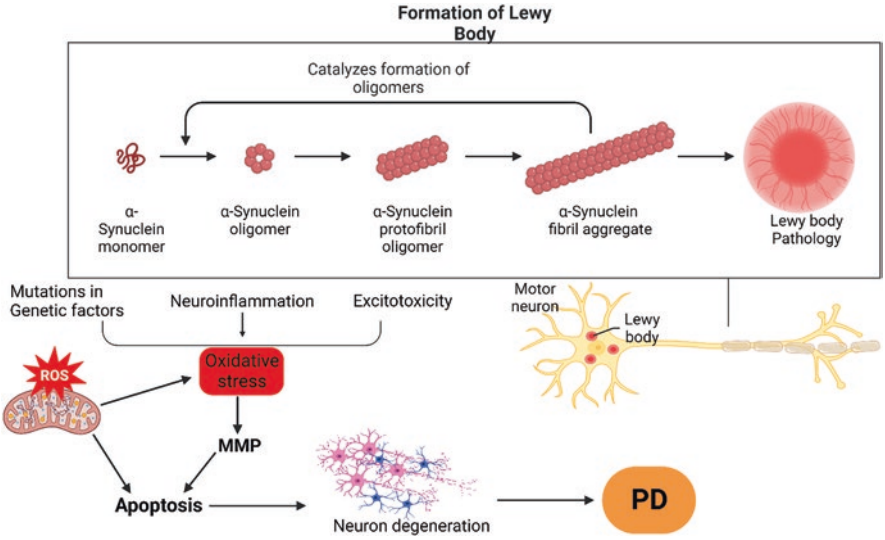

Fig. 1.2 Pathology of PD. The α-synuclein monomers undergo a process of aggregation, transitioning from individual molecules to α-synuclein oligomers. These oligomers then further assemble into fibrils. This sequence of events ultimately contributes to the development of Lewy body (LB) pathology, a hallmark of PD. The deposition of LBs within motor neurons precipitates neuronal dysfunction. Mutations in genetic factors are implicated in the disease's onset. Additionally, neuroinflammation and excitotoxicity in neurons lead to increased oxidative stress. This, in turn, triggers dysfunction in mitochondria; as a consequence, the mitochondrial membrane potential is disrupted. Ultimately, these cellular disturbances culminate in apoptotic processes, resulting in the degeneration of neurons

stages to become harmful as the disease progresses (Hirsch and Hunot 2009) (Fig. 1.2).

1.2.2.1 Susceptibility of Neurons

The intricate web of neurodegenerative marks seen in PD demonstrate a specific susceptibility of midbrain neurons adorned with the enigmatic neuromelanin. These prized neurons reside within the bustling realm of the ventral tier of the SNc, which are rich in dopamine transporter but their energy machinery, the glycolytic enzymes, remains in meager supply. Calbindin, a neuroprotective steward and alert guard against the assault of calcium ions, is curiously lacking from these cells. All of them are projection neurons with unmyelinated or insufficiently myelinated long, thin axons. Increased iron content may be connected to the selective sensitivity of A-9 nigral neurons, rendering them more susceptible to oxidative stress (Zhou et al. 2010; Lv et al. 2011; Sian-Hulsmann et al. 2011).

SN neurons with advanced degeneration showed a considerable drop in intracellular pigment, while those with normal morphology display a rise in pigment density linked to greater levels of α-syn. This emphasizes the early neuromelanin alteration's selectivity for A-9 neurons and the absence of such changes in other

melanin-containing neurons in the early PD in the A-10 areas (Halliday et al. 2005). Iron enhances α-syn aggregation and controls its expression at the translational stage (Febbraro et al. 2012; Levin et al. 2011). However, the upregulated levels of iron result in the overexpression of α-syn, which causes their selective loss (Fasano et al. 2006; Guerrero et al. 2013). Under oxidative conditions, increased α-syn concentrations near pigment-associated lipids may set off a chain of events that result in intracellular α-syn aggregates and the dispersal of protective pigments, which accelerates cell death (Lv et al. 2011; Halliday et al. 2005; Ruiperez et al. 2010).

PD-affected SNc neurons exhibit diminished brain-derived neurotrophic factor (BDNF) expression. The immunohistochemistry revealed almost 20% depletion of glial cell line-derived neurotrophic factor (GDNF) and loss of BDNF within both neuron bodies and their surrounding neuropil as revealed by Chauhan and colleagues in 2001, but enhanced the figures of BDNF and neurotrophin-3 immunoreactive microglia swarming around the beleaguered neurons (Knott et al. 2002), whereas biochemistry reveals no depletion of GDNF in the nigrostriatal regions of PD subjects (Mogi et al. 2001).

The mitochondrial impairment emerges as a pivotal player in the depletion of neurons. A distinctive surge in mitochondrial DNA deletions within the SN and other cerebral regions of PD-afflicted brains, relative to age-matched controls, underscores that the impairment of mitochondria is not confined to the SN alone (Gu et al. 2002). This highlights that mitochondrial dysfunction extends beyond the confines of the SN, suggesting that various brainstem clusters are impacted, although dopaminergic SN neurons showcase a more pronounced dependence on mitochondrial bioenergetics and oxidative phosphorylation. Early in the passage of PD, there is a decline in brain mitochondrial metabolism, but it is uncertain whether this is a prime or subsequent event (Winslow and Rubinsztein 2011).

1.2.3 Huntington's Disease

HD is an inherited neurodegenerative ailment that unveils a distressing triad of advancing motor incapacities, cognitive decline, and emotional irregularities (Rather et al. 2023). This affliction is kindled by an undesirable repetition of CAG segments in the huntingtin gene, which leads to an abnormal form of the huntingtin protein (Bogomazova et al. 2019). This protein's pervasive presence spans the expanse of the brain, orchestrating an intricate symphony of various cellular functions. The pathophysiology of HD is complex and involves both the accumulation of the altered huntingtin protein and the interruption of a multitude of molecular pathways (Snowden 2017). In the brain, the mutant protein accumulates in areas such as the nucleus and striatum, leading to the development of aggregates and the deterioration of neurons. This in turn leads to a series of events including reduced neurotransmission, altered energy metabolism, and inflammation (Bogomazova et al. 2019). The end result is the progressive neuronal damage and the disruption of neural circuits throughout the brain, which results in the characteristic clinical symptoms of HD.