MULTIDISCIPLINARY APPROACH IN MEDICAL SCIENCE III

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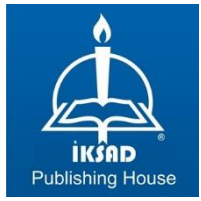

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CONTENTS

PREFACE

Science is the lost property of humanity. Mankind has made great efforts to reach science and science since its existence. Today, research studies continue in order to reach science and produce knowledge. Very valuable scientists are in the race to take science to the next level by checking the existing information. In this way, in addition to coping with difficulties, it becomes possible to reach new information and make new discoveries in every field.

This book, which includes valuable chapters in the field of medicine and health sciences, consists of 10 chapters. We are happy to share our book with the scientific community and our readers. I heartily congratulate our esteemed writers, who put their valuable works into the service of humanity as a reward for a great effort.

We dedicate this book, which includes very valuable topics, to the doctors and their families who lost their lives in the 6 February 2023 earthquake. We commemorate our martyrs with mercy. Bless their souls.

I would like to thank the İKSAD Publishing family, scientific committee, authors and readers who contributed to the preparation, arrangement and publication of the book.

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CHAPTER 6

BIOCHEMICAL PERSPECTIVE ON PARKINSON'S DISEASE

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1. PARKINSON'S DISEASE - DEFINITION

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that affects the nervous system and primarily affects movement. It is characterized by the degeneration and loss of dopamine-producing neurons in a part of the brain called the substantia nigra. The resulting dopamine deficiency in the brain leads to a range of motor symptoms, including tremors, rigidity, bradykinesia (slowness of movement), and postural instability. Parkinson's disease can also cause non-motor symptoms, such as depression, anxiety, sleep disturbances, and cognitive impairment. Parkinson's disease is typically diagnosed in people over the age of 60, but it can also affect younger people. Although there is currently no cure for Parkinson's disease, treatments are available to help manage the symptoms and improve quality of life (Ciofalo et al., 2019).

Parkinson's disease is named after James Parkinson, an English physician who first described the condition in 1817. His work, titled "An Essay on the Shaking Palsy," provided a detailed clinical description of the motor symptoms associated with the disease.In the late 19th and early 20th centuries, several researchers made significant contributions to the understanding of Parkinson's disease. Jean-Martin Charcot, a French neurologist, further expanded on the clinical description and classification of the disease, emphasizing the characteristic tremors and rigidity (Goetz, 2011).

2. THE REASONS OF PARKINSON'S DISEASE

The exact causes of Parkinson's disease are not yet fully understood, but it is believed to be a combination of genetic and environmental factors. Here are some of the possible reasons for Parkinson's disease:

Genetics: In some cases, Parkinson's disease may be inherited. Researchers have identified several genetic mutations that are associated with the development of the disease. Most Common genes related to Parkinson's Diseases are VPS35, LRRK2, PARK7, PINK1,PARK2,SNCA (Cherian & Divya, 2020).

Environmental factors: Exposure to certain toxins, such as pesticides, herbicides, and industrial chemicals, has been linked to an increased risk of Parkinson's disease (Goldman, 2014).

Age: Parkinson's disease is more common in older adults, and the risk of developing the disease increases with age (Emami Kazemabad et al., 2022).

Gender: Men are more likely to develop Parkinson's disease than women (Cerri, Mus, & Blandini, 2019) .

Head trauma: People who have experienced head injuries may have a higher risk of developing Parkinson's disease (Bower et al., 2003).

Inflammation: Chronic inflammation in the brain may contribute to the development of Parkinson's disease (Pajares, A, Manda, Bosca, & Cuadrado, 2020).

Oxidative stress: This is a process that occurs when there is an imbalance between free radicals and antioxidants in the body. Oxidative stress can damage cells in the brain and contribute to the development of Parkinson's disease (Subramaniam & Chesselet, 2013).

It is important to note that having one or more of these risk factors does not necessarily mean that a person will develop Parkinson's disease. The disease is complex, and more research is needed to fully understand the causes and contributing factors.

3. PARKINSON'S DISEASE SYMPTOMS

The symptoms of Parkinson's disease can vary from person to person, and may include both motor and non-motor symptoms (Sveinbjornsdottir, 2016). Some of the common symptoms of Parkinson's disease include:

Tremors: Tremors or shaking, typically in the hands, fingers, arms, or legs, are a hallmark symptom of Parkinson's disease.

Rigidity: Stiffness or rigidity in the muscles, which can make it difficult to move and may cause pain.

Bradykinesia: Slowness of movement, which can make simple tasks such as buttoning a shirt or walking difficult.

Postural instability: Impaired balance and coordination, which can increase the risk of falls.

Non-motor symptoms: Parkinson's disease can also cause non-motor symptoms such as depression, anxiety, sleep disturbances, cognitive impairment, and autonomic dysfunction (problems with blood pressure, heart rate, and digestion).

Micrographia: Small handwriting

Masked face: Reduced facial expression or a "mask-like" appearance.

It is important to note that not all people with Parkinson's disease will experience all of these symptoms, and the severity of symptoms can vary depending on the individual. In addition, some symptoms may worsen over time as the disease progresses. If you are experiencing any of these symptoms, it is important to see a healthcare provider for an evaluation (Eklund et al., 2022).

4. NEUROPATHOLOGY OF PARKINSON'S DISEASE

The neuropathology of Parkinson's disease involves the progressive degeneration of specific regions in the brain, particularly in the midbrain, where the substantia nigra is located. This leads to the loss of dopamine-producing neurons, which are critical for the regulation of movement and motor function. One of the hallmark neuropathological features of Parkinson's disease is the accumulation of a protein called alpha-synuclein in the brain. Alpha-synuclein is normally present in the brain and is involved in the regulation of synaptic function, but in Parkinson's disease, it forms abnormal clumps called Lewy bodies, which are found in the neurons of affected brain regions. The loss of dopamine-producing neurons and the accumulation of Lewy bodies in the brain are believed to disrupt the normal functioning of brain circuits that regulate movement, leading to the motor symptoms of Parkinson's disease such as tremors, rigidity, and bradykinesia. In addition to the loss of dopamine-producing neurons and the accumulation of Lewy bodies, other neuropathological features of Parkinson's disease include inflammation and oxidative stress, which can contribute to the degeneration of neurons (Dickson, 2018).

Another neuropathological changes in dopaminergic neurons includes degeneration of dopaminergic neurons,loss of dopaminergic transporters and changes in neurotransmitters.

Degeneration of Dopaminergic Neurons: Parkinson's disease is characterized by the selective degeneration of dopaminergic neurons in the substantia nigra. These neurons produce dopamine, a neurotransmitter critical for motor control. As the disease progresses, there is a progressive loss of these neurons, resulting in a significant reduction in dopamine levels in affected brain regions (Ikeda, Ebina, Kawabe, & Iwasaki, 2019).

Loss of Dopamine Transporters: Dopamine transporters are proteins responsible for reuptake of dopamine from the synaptic cleft. In Parkinson's disease, there is a significant loss of dopamine transporters, which can be visualized using imaging techniques like single-photon emission computed tomography (SPECT) or positron emission tomography (PET) scans. This loss reflects the degeneration of dopaminergic neurons (Ikeda et al., 2019).

Changes in Another Neurotransmitter Levels

Acetylcholine: Acetylcholine is another neurotransmitter involved in motor control. In Parkinson's disease, there is an imbalance between dopamine and acetylcholine levels, with an increase in acetylcholine activity due to the loss of dopaminergic inhibition. This imbalance contributes to the motor symptoms and disrupts the delicate balance necessary for smooth motor function (Bono et al., 2021).

Serotonin: Serotonin is a neurotransmitter that plays a role in mood regulation and other functions. Changes in serotonin levels have been observed in Parkinson's disease and may contribute to non-motor symptoms such as depression, anxiety, and sleep disturbances (Suratos, Del Rosario, & Jamora, 2020).

Noradrenaline (Norepinephrine): Noradrenaline is involved in regulating attention, arousal, and blood pressure. It has been found that there is a loss of noradrenaline-producing neurons in certain brain regions in Parkinson's disease. These changes may contribute to non-motor symptoms such as orthostatic hypotension (low blood pressure upon standing) and fatigue (Cacabelos et al., 2021).

Glutamate: Glutamate is the primary excitatory neurotransmitter in the brain. In Parkinson's disease, there are changes in glutamate levels and signaling, including increased glutamate release and altered glutamate receptor activity. These changes can contribute to excitotoxicity, a process that leads to neuronal damage and death, further exacerbating the neurodegenerative process (Lyu et al., 2021).

The interplay and imbalance between these neurotransmitters, particularly the dopamine-acetylcholine system, play a significant role in the motor symptoms of Parkinson's disease. Other neurotransmitters, such as serotonin, noradrenaline, and glutamate, contribute to non-motor symptoms

and the overall pathophysiology of the disease. Understanding these neurotransmitter changes is important for developing therapeutic strategies aimed at restoring neurotransmitter balance and managing the symptoms of Parkinson's disease**.**

Overall, the neuropathology of Parkinson's disease is complex and involves a combination of genetic and environmental factors, as well as changes in brain chemistry and the accumulation of abnormal proteins. Understanding the neuropathology of Parkinson's disease is important for the development of new treatments and therapies that can slow or halt the progression of the disease.

5.PATHOGENESIS OF PARKINSON'S DISEASE

5.1 Oxidative Stress -Inflammation and Mitochondrial Dysfunction

Oxidative stress, inflammation, and mitochondrial dysfunction are interconnected processes that can influence and exacerbate each other, contributing to various diseases, including neurodegenerative disorders like Parkinson's disease. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize and repair their damaging effects. ROS, such as free radicals, can cause cellular damage and trigger inflammation. In the context of Parkinson's disease, oxidative stress plays a significant role in the progressive degeneration of dopamine-producing neurons. The high energy demands of neurons make them particularly vulnerable to oxidative damage. Inflammation is the body's response to injury, infection, or other harmful stimuli. In the case of Parkinson's disease, chronic inflammation is believed to contribute to neurodegeneration. Activated immune cells release pro-inflammatory molecules, such as cytokines and chemokines, which can further induce oxidative stress. The inflammatory response in the brain can also activate microglia, the immune cells of the central nervous system, which can produce toxic substances that damage neurons. Mitochondrial dysfunction refers to abnormalities in the function and structure of mitochondria, the powerhouses of the cells responsible for energy production. Mitochondria are crucial for neuronal health, and any disruption in their function can lead to energy deficits, increased ROS production, and impaired cellular processes. In Parkinson's disease, dysfunctional mitochondria have been observed in affected brain regions and are thought to contribute to the degeneration of

dopamine neurons.The relationship between these processes is complex and interconnected. Oxidative stress can induce mitochondrial dysfunction by impairing mitochondrial DNA, enzymes, and membrane integrity, leading to reduced energy production and increased ROS generation. Mitochondrial dysfunction, in turn, can lead to increased oxidative stress as a result of impaired electron transport chain function. Both oxidative stress and mitochondrial dysfunction can trigger inflammatory responses, while inflammation, through the release of pro-inflammatory molecules, can exacerbate oxidative stress and further impair mitochondrial function. These processes create a vicious cycle, where oxidative stress, inflammation, and mitochondrial dysfunction reinforce and amplify each other, ultimately leading to progressive neuronal damage and the development and progression of diseases like Parkinson's disease. Understanding and targeting these interconnected processes may hold promise for developing therapeutic strategies to mitigate the progression of neurodegenerative disorders (Wang, Wang, Gao, & Sun, 2022).

5.2 Excitotoxicity

Excitotoxicity is a phenomenon that involves excessive activation of excitatory neurotransmitters, particularly glutamate, leading to neuronal damage or death. While excitotoxicity is primarily associated with conditions like stroke and neurodegenerative diseases, emerging evidence suggests its involvement in Parkinson's disease as well. In Parkinson's disease, excitotoxicity is believed to play a role in the degeneration of dopamine-producing neurons in the substantia nigra, a brain region involved in motor control. The imbalance between excitatory and inhibitory neurotransmission, with excessive glutamate signaling, can result in prolonged and excessive activation of glutamate receptors, particularly N-methyl-D-aspartate (NMDA) receptors. Several factors contribute to excitotoxicity in Parkinson's disease. One of the key factors is the dysfunction of the glutamate transporters responsible for removing excess glutamate from the synaptic cleft. Impaired glutamate reuptake can lead to an accumulation of glutamate, which further enhances excitotoxicity. Additionally, the loss of dopamine, a neurotransmitter that helps regulate glutamate release and excitatory signaling, can disrupt the balance of excitatory and inhibitory neurotransmission. Excitotoxicity triggers a cascade of events within neurons, including calcium influx and activation of various enzymes and pathways, ultimately leading to neuronal dysfunction and death. The excessive calcium influx activates enzymes such as

phospholipases, proteases, and nitric oxide synthase, which can damage cellular components, disrupt energy metabolism, and generate ROS. These processes contribute to oxidative stress and further neuronal damage. Furthermore, excitotoxicity can induce mitochondrial dysfunction, impairing the ability of mitochondria to produce ATP and regulate calcium homeostasis. Dysfunctional mitochondria produce more ROS, contributing to oxidative stress and exacerbating neuronal damage.To counteract excitotoxicity, the brain employs various protective mechanisms, including the release of inhibitory neurotransmitters like gamma-aminobutyric acid (GABA) and the activation of anti-excitotoxic pathways. However, in Parkinson's disease, these compensatory mechanisms may be overwhelmed or impaired, leading to a heightened susceptibility to excitotoxicity. Targeting excitotoxicity is an area of active research for potential therapeutic interventions in Parkinson's disease. Strategies include developing drugs that modulate glutamate receptors, enhancing glutamate clearance mechanisms, and promoting the activation of neuroprotective pathways to mitigate the damaging effects of excessive glutamate signaling. Overall, while excitotoxicity's role in Parkinson's disease is still being elucidated, evidence suggests that it contributes to the degeneration of dopamine neurons and may represent a potential target for therapeutic interventions (Iovino, Tremblay, & Civiero, 2020).

6. Diagnosing Parkinson’s Disease and Treatment Guidelines

Diagnosis of Parkinson's disease usually involves a combination of clinical evaluation, medical history, and physical examination. There is no specific test for Parkinson's disease, but healthcare providers may use certain tests, such as imaging studies like MRI or DaTscan, to rule out other conditions that may cause similar symptoms. Diagnosis of Parkinson's disease is usually made based on the presence of two or more of the hallmark motor symptoms, such as tremors, rigidity, bradykinesia, and postural instability. Treatment of Parkinson's disease is focused on managing symptoms and improving quality of life. There are several medications that can help increase dopamine levels in the brain and improve motor symptoms, such as levodopa and dopamine agonists. In addition to medications, physical therapy and exercise can also be beneficial for improving mobility and reducing stiffness and rigidity. For more advanced cases, deep brain stimulation (DBS) surgery may be an option. DBS involves implanting a small electrode into the brain that delivers electrical impulses to targeted areas, which can help alleviate

symptoms such as tremors, rigidity, and dyskinesia (involuntary movements). It is important to note that there is currently no cure for Parkinson's disease, and treatments are focused on managing symptoms and improving quality of life. In addition to medical treatments, support groups, counseling, and lifestyle modifications such as a healthy diet and regular exercise may also be helpful for people with Parkinson's disease (Rizek, Kumar, & Jog, 2016).

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