Proceedings of the 2nd International Conference on Environmental Geoscience and Earth Ecology
DOI: 10.54254/2753-8818/47/2024PJ0101

The pathogenesis and treatment of Parkinson's disease

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Abstract. Parkinson's disease (PD) is a neurodegenerative disease that primarily affects middle-aged and older adults. Its incidence is second only to that of Alzheimer's disease. The primary source of clinical symptoms is the degradation and death of dopaminergic neurons in the substantia nigra-striatum. Patients mainly show motor symptoms such as static tremor, rigidity, bradykinesia and postural instability, and non-motor symptoms such as sensory disturbance, autonomic nervous dysfunction and mental cognitive impairment. There is no proven way to cure the disease or to slow its progression through neuroprotection, therefore treatment focuses mostly on treating symptoms. This study examines the shared pathophysiology of PD, which includes inflammation, abnormalities in protein handling, oxidative stress, and mitochondrial dysfunction. Next it discusses the available PD treatment options, which include standard medication therapy, promising surgical procedures, gene therapy, and new approaches to individualized PD care. The safety and usefulness of many treatments are still unknown, though. Hope that as life science and technology advance, the etiology of Parkinson's disease will become clearer and more dependable treatment options will be created to enhance sufferers' quality of life.

Keywords: Parkinson’s disease, neurodegenerative diseases, parkinsonism.

1. Introduction

Parkinson’s Disease is a neurodegenerative disease common in middle-aged and elderly people, and its incidence ranks second among all neurodegenerative diseases. The primary pathogenic alteration in PD is the degeneration and death of dopaminergic neurons in the substantia nigra. Clinical symptoms include bradykinesia, myotonia, resting tremor, and postural balance dysfunction. The number of people with Parkinson's disease has significantly increased along with the exacerbation of population aging, the growth in average life expectancy, and changes in human living environments. This has increased demand for medical resources and social productivity across society. Epidemiological study indicates that a multitude of internal and external characteristics, such as time, region, race, age, and gender, are associated with the population's vulnerability to PD. The majority of instances are caused by genetic variation controlling metabolic pathways and exposure to the environment [1]. The association between PD and these influencing elements, however, cannot be explained by a specific pathogenesis, which has sparked active study on the pathogenesis of PD in society.

The pathophysiology of PD is the subject of several ideas, the most widely recognized of which include oxidative stress, abnormal protein treatment, inflammation, and mitochondrial dysfunction [2]. There are numerous PD therapy options available, but there is no proven cure for the condition. Drugs

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and treatments can only partially manage a patient's symptoms; they cannot stop the disease from progressing further; and there is no way to fully recover from PD. Additionally, there could be a lot of adverse effects, which pose a concealed risk to the patient's quality of life. Furthermore, the ability of patients to receive long-term, successful therapy will also depend on their financial status and the quality of care provided by nearby hospitals. Therefore, finding more practical, affordable, and effective treatment methods for medical work is also a pressing issue.

The research on the pathogenesis of PD will help medical staff to deepen their understanding of the nature of PD, so as to diagnose patients individually, and then they will also be better able to tailor initial treatment plans to each patient's unique circumstances or come up with the most targeted new treatment plan, so as to effectively improve symptoms and improve work ability and quality of life. This paper provides a detailed summary of the pathophysiology of PD, followed by a discussion of the disease's treatment options from the perspectives of medicine, surgery and gene, and a prospecting of future developments based on ongoing research.

2. Pathogenesis

2.1. Oxidative stress (OxS)

Reactive oxygen species (ROS) are compounds having oxygen in their molecular composition and particularly active chemical characteristics, and they are a major pathogenic factor in Parkinson's disease. Under normal conditions, ROS play a vital part in the execution of cell physiological tasks such as growth, differentiation, and death. However, when OxS develops, that is, when cell oxidation and antioxidation are out of balance, oxygen-containing free radicals are created in huge amounts, which cannot be properly removed and accumulate in the body. Free radicals act on dopaminergic neurons in substantia nigra, causing damage to their functions and structures, and the location where ROS is produced determines the damage sites, such as lipids, protein, DNA, RNA, etc. Neurons will eventually degenerate and die when there is significant damage to the integrity of the cells [3]. Trace elements, vitamins, and enzymes are only a few of the biochemical components that are linked to ROS generation. The primary generator of ROS in vivo is NADPH oxidase (NOX), and nuclear factor E2-related factor 2 (Nrf2) is crucial for the body's defense against OxS in humans. Moreover, selenium and heme oxygenase-1 (HO-1) also have certain neuroprotective properties [4]. It is possible to identify possible therapeutic targets and present novel therapeutic approaches by thoroughly examining antioxidant factors and the genes that control their function.

2.2. Mitochondrial dysfunction

Mitochondria is the main place for cell energy supply, which is intimately linked to a number of physiological processes. Abnormalities in several physiological processes, such as reduced energy production, ROS production, and stress-induced apoptosis, can result from its failure. Neurodegenerative illnesses like PD frequently exhibit mitochondrial dysfunction due to the high energy demand of neurons and the high unsaturated fatty acid content of brain tissue, which makes it susceptible to ROS damage. Mitochondrial electron transport chain damage, alterations in mitochondrial morphology and dynamics, mutations in mitochondrial DNA, and aberrant calcium homeostasis are among the dysfunctions implicated in PD [5]. In addition, genetic factors also play an important role in the pathogenesis of PD. Gene mutations can induce various functional disorders of familial Parkinson's disease. Common mutant genes include DJ-1, CHCHD2, PINK1, Fbxo7, Parkin, etc. The different clinical parameters shown by these genes can help with the early diagnosis and personalized treatment of PD.

2.3. Abnormalities in protein handling

The formation of Lewy corpuscles is an important pathophysiological change of PD, and α -synuclein (α-Syn) is its main component. Under normal circumstances, cells have an internal monitoring mechanism to regulate the processing or clearance of protein, but the autophagy-lysosomal system and

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ubiquitin-proteasome system function of PD patients are impaired, the ability to selectively degrade abnormal or misfolded protein is reduced, and the degradation of α-Syn is also inhibited. In addition, some studies have shown that the mutation of GBA1 gene will lead to the lack of lysosomal enzyme acid β-glucose-cerebrosidase (GCase), which promotes the formation of α-Syn and forms a vicious circle, which eventually leads to the increase of α-Syn at the cell level and a large number of aggregation [6,7].

2.4. Inflammation

Inflammation related to PD includes neuroinflammation and intestinal inflammation. Neuroinflammation is an immune response that plays an important role in protecting neurons, but it may also cause damage to neurons and promote the development of neurodegenerative diseases. It is found that the activation of immune cells such as microglia and astrocytes is an important part of the pathogenesis of PD patients, accompanied by the regulation of cytokines and chemokines. α-Syn has the ability to activate microglia, which then engulf it. This process spreads across the entire brain and eventually causes dopaminergic neurons to degenerate [8]. Intestinal inflammation is also connected to the pathophysiology of PD. According to research, people with PD had higher expression of some genes encoding HLA, but lower expression of other HLA types. A study on inflammatory bowel disease (IBD) also revealed comparable findings [8]. Patients with IBD are more likely to develop PD, according to survey data, which is consistent with the theory that intestinal inflammation may contribute to PD. The brain-gut axis may have anything to do with these results. According to the theory of the brain-gut axis, certain microorganisms in the gut can penetrate the mucosal barrier of the gut, cause α-Syn to be expressed by intestinal endocrine cells, create a neuroepithelial circuit that connects the gut to the brain stem by means of synapses with the vagus nerve, and ultimately transfer information to the brain's dorsal motor nucleus [9].

The occurrence of PD is caused by the degeneration and death of DA neurons, and the massive aggregation of a-Syn is an important pathological change. The mechanism of PD involves OxS, mitochondrial dysfunction, protein's abnormal treatment and inflammation. An in-depth understanding of the occurrence process of PD will help people to understand the characteristics of PD more accurately and optimize its treatment plan.

3. Therapeutic methods

3.1. Drug therapy

Traditional anti-PD drugs can be mainly divided into two categories: dopaminergic drugs and anticholinergic drugs. The equilibrium between the dopaminergic and cholinergic nervous systems can be restored to play a therapeutic role by either raising or lowering the activity of dopaminergic neurons. Levodopa, a precursor to dopamine, is the most widely used medication for PD. Its ability to pass the blood-brain barrier allows it to increase dopamine production from patients' injured dopaminergic neurons, which serves to alleviate symptoms. Carbidopa, which is frequently taken in conjunction with levodopa, is an inhibitor of peripheral dopa decarboxylase. Because it can lessen levodopa metabolism in peripheral tissues, minimize adverse effects, and simultaneously increase the quantity of levodopa that enters the center, carbidopa can improve the effects of the medication. Alternatively, dopamine can be substituted with dopamine receptor agonists to fulfill a physiological function.

Monoamine oxidase aldehyde dehydrogenase B (MAO-B) and catechol -O methyltransferase (COMT) inhibitors, anticholinergic medications, and antipsychotic medications are examples of alternative medications. Every medication has unique mechanisms of action and indications. To create customized treatment regimens, it is essential to determine the kinds, dosages, and administration techniques of medications based on the unique medical characteristics of each patient [2]. However, drug therapy also has great limitations, and with the progress of the disease, effectiveness may progressively wane. For example, the efficacy of levodopa will gradually weaken with the degeneration of dopaminergic neurons in the brain. If you want to maintain the original efficacy by increasing the

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dosage of the drug, you need to pay the price of increasing the side effects. In addition, levodopa therapy may potentially worsen the build-up of cytotoxic ROS, which could cause more neuronal damage and make it more difficult for the medication to have a beneficial therapeutic effect over the long run [10].

3.2. Surgical therapy

3.2.1. Deep brain stimulation (DBS)

The fundamental idea behind DBS is to implant electrodes in a particular part of the patient's body and then continually apply electrical stimulation to the brain lesions in order to alleviate the patient's clinical symptoms. The subthalamic nucleus, ventral intermediate thalamic nucleus, and medial globus pallidus are frequently surgical targets. Because DBS is reversible, adjustable, safe and minimally invasive, it is often chosen by PD patients. When implanting electrodes, it is imperative to prevent infection of the implanted equipment. In order to provide a long-lasting and sustained course of therapy, electrodes—the primary therapeutic component of DBS—must also possess strong biological adaptability to prevent inflammatory foreign body reactions. Numerous novel stimulation techniques have been created in recent years by researchers, such as the introduction of controlled current IPG, novel waveforms for stimulation, and novel timing patterns for stimulation [11]. Further research is still necessary to determine its clinical efficacy.

3.2.2. Cell replacement therapies

Cell replacement treatment is the medical practice of implanting new cells into patients to replace those that have been damaged by illnesses, hence restoring the body's impaired function. Replacing the corresponding sick cells with homologous cells is one of the simplest concepts. Researchers in the past attempted to transplant fetal ventral midbrain (fVM) cells. Patients' motor complaints have improved and the on-off phenomenon has somewhat subsided following fVM transplantation. The number of fetuses, the transplantation route, the recipient's state, and the source of the graft all affect the therapeutic impact upon implantation [12]. Still, there are a few issues like hemorrhage, graft-induced dyskinesia, and a poor survival rate. PD can also be treated using stem cells. Epidermal stem cells (ESCs), neural stem cells (NSCs), mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and so forth are examples of selectable stem cells. Stem cell-derived cells are more accessible than fVM cells, but there are still a number of significant issues, including the possibility of tumorigenicity, the immunosuppressive effect, the off-target effect, and technical issues with surgical delivery devices [13].

3.3. Gene Therapy

Gene therapy is a rapidly developing new field in recent years. Its basic principle is to transport DNA, RNA, antisense oligonucleotide, DNA or RNA editing enzyme to the brain of PD patients by using adeno-associated virus or other vectors to realize the normal expression of genes. By regulating the expression of related genes, the level of essential enzymes involved in dopamine synthesis can be improved, and then the content of dopamine can be restored. Gene therapy can also provide enhanced neurotrophic support to improve the survival rate of DA neurons. For GBA1-related PD, gene therapy can restore the activity of GCase and reduce the accumulation of toxic and pro-inflammatory glycolipid substrates, thus reducing the aggregation of α-Syn [14]. In addition, gene therapy can also be used to regulate the interaction between different segments of basal ganglia, and inhibit the activity of subthalamic nucleus by promoting the synthesis of inhibitory neurotransmitter γ-aminobutyric acid (GABA), thus improving the symptoms of PD patients [15]. In summary, each treatment approach has benefits and drawbacks of its own. Treatment plans must be customized for each patient, taking into account both their motor and non-motor symptoms. This will allow for a reduction in medication dosage, which will minimize side effects and consequences. On the basis of routine drug treatment, other treatment methods such as surgery are used as effective supplements, thus effectively improving symptoms and improving patients' workability and quality of life. We should not only base ourselves on the present, but also consider the patient's benefit in the long run to choose the treatment method.

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4. Conclusion

As the second largest neurodegenerative disease in the world, the research progress of PD has been widely concerned by the public. This paper summarizes the main pathways of PD, followed by a discussion of the various treatments for PD. Its pathophysiology is intricate and includes OxS, abnormalities in protein handling, mitochondrial malfunction, inflammation, and other factors. For the loss of DA neurons, there are several therapeutic options. In addition to conventional medication therapy, new surgical techniques like gene therapy, cell replacement therapy, and DBS have also been developed. Through the integration and induction of the above contents, medical staff can understand the whole pathogenesis of PD more deeply and put forward the most suitable individualized treatment plan for patients. However, the details of the link between different pathologies require further exploration. Traditional medication therapy can help patients feel better, but it cannot stop the condition from getting worse. DBS is a successful therapeutic approach, but doctors' expertise is needed to maximize the advantages and minimize problems. New treatments like gene therapy and cell replacement therapy can cure PD at its root cause, however, issues like immunological rejection and ethics must be taken into consideration. These will require more study and development on the part of medical professionals. It is hoped that with the continuous development of life science and technology, researchers can further clarify the pathogenesis of PD and propose more effective treatment methods so that human beings can better cope with PD in a society with an aging population and rising incidence.

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