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PARKINSON'S DISEASE: A MULTITUDE OF BRAIN DISTURBANCES

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ABSTRACT

Parkinson's disease (PD) is the most widespread neurodegenerative disease following Alzheimer's disease (AD). An increased risk of the disease has been observed due to exposure to environmental pollutants and prior traumatic brain damage. PD presents with motor disorders and other disabling symptoms, such as cognitive deterioration, mood changes, depression, muscle stiffness, and tremors, that can predict the arrival of the disease. Symptoms manifest with balance disorders, uncertainty in walking, hunched posture, and slowness in speaking, amongst others. The neurodegeneration that occurs in PD is mediated by dysfunctions that fuel the pathological state. There is neuronal degeneration of the substantia nigra with a reduction in dopamine levels, a lower concentration of neuromelanin, and a reduction of mitochondrial respiratory activity. Various factors are involved in the disease and contribute to abnormal immunological and inflammatory reactions. The immune disorder that occurs involves microglia in the brain and other cells, causing the release of inflammatory cytokines and chemokines, which contributes to the death of dopaminergic neurons and destroys the blood-brain barrier, with infiltration of toxic substances into the brain. Microglia have pattern recognition receptors that bind abnormal proteins that enter the brain to eliminate them. Damage-associated molecular patterns (DAMPs) bind toll-like receptors (TLRs) and activate the NF-kB pathway with the secretion of cytokines such as TNF, IL-1, IL-6, and the chemokine CCL-2, contributing to the pathogenesis of PD.

KEYWORDS: *Parkinson's disease, neurodegeneration, brain, immune, inflammation, dopamine*

INTRODUCTION

Parkinson's disease (PD) affects approximately 1% of people over the age of 65 in industrialized countries (1). The disease was first described by the English physician James Parkinson in 1817 as "shaking palsy" (2). PD is a complex multifactorial and progressive disease that leads to other brain disorders, including immune dysfunction that results in neuroinflammation. In recent decades, much progress has been made regarding the pathogenesis of the disease. However, many points remain unclear, and therefore, further studies are required.

After Alzheimer's disease (AD), PD is the most common neurodegenerative disorder affecting the populations of industrialized countries (3). It is an idiopathic disease with an unknown cause and is not accompanied by other disease

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processes. PD is also a genetic disease; in fact, several mutated genes are involved (4). The pathology occurs due to the loss of cells that produce the neurotransmitter dopamine.

PD presents with the following cardinal symptoms: muscle rigidity of the neck, trunk, and limbs, tremors (also visible from head movement), bradykinesia, speech and swallowing impairment, postural instability, dystonia, shuffling gait, loss of smell, death of neurons, and balance disorders, which are symptoms that can increase in case of psychological difficulties such as anxiety. Non-motor symptoms that appear early at the beginning of the disease could lead to faster diagnosis of PD (5). Moreover, the PD patient may suffer from depression and slowness in verbal expression.

The disorder is characterized by the loss of dopaminergic neurons of the substantia nigra pars compacta, with a lower concentration of melanin, reduction of dopamine, and a long course (6). Dopamine is an important neurotransmitter that allows for communication between nerve cells in the brain. In PD patients, there is a lower activity of alpha-ketoglutarate dehydrogenase, an enzymatic complex belonging to the class of oxidoreductases, participating in the Krebs cycle (7,8). Therefore, there is a reduction in mitochondrial activity and the loss of Lewy body protein inclusions in the PD patient (9).

The causes of the disease are diverse, including environmental and genetic factors, but also brain lesions, infections, brain neurotoxins, and oxidative damage. It appears that individuals who take xanthine derivatives, such as caffeine or theophylline, have a reduced risk of neurodegenerative disease (10). One interesting theory claims that PD is caused by misfolded proteins in the brain, as happens with prions (11). The disease has been seen to worsen in polluted environments and with advanced age (12, 13), two elements that coincide with the dysfunction of the immune system (Table I).

Table I. *Some factors that may contribute to Parkinson's disease (PD) pathology.*

Contributing factors:		
▪ mitochondrial dysfunction	▪ brain lesions, infections	▪ DNA methylation
▪ lower alpha-ketoglutarate dehydrogenase activity	▪ brain neurotoxins	▪ histone modifications
▪ environmental and genetic factors	▪ oxidative damage	▪ altered microRNA expression
▪ sleep disorders		
Risk factors:		
▪ pesticides	▪ alcohol consumption	▪ place of residence
▪ heavy metals	▪ diet	▪ lifestyle
▪ industrial chemicals	▪ vitamin D	▪ professional activity
▪ foods rich in animal fats (saturated or unsaturated)	▪ smoking	

In recent years, many pharmacological therapeutic improvements have been made, although the progressively worsening course of PD makes it difficult to treat. The interactions between an altered immune system, unfavorable environmental factors, and ageing can lead to PD pathology. In this disorder, innate immunological activation can occur through pathogen-associated molecular patterns (PAMPs), and self-originated damage-associated molecular patterns (DAMPs) which can induce “sterile inflammation” through the toll-like receptors (TLR)s (14). Microglia have pattern recognition receptors such as TLR2, TLR4 and TLR6, that bind abnormal proteins that enter the brain to eliminate them.

The alteration of the immune system can involve both T and B cells with the production of autoantibodies. The cerebral lymphatic ducts are rich in B cells, T cells, and antigen-presenting cells, which protect the central nervous system (CNS) from external insults and endogenous changes. Molecules foreign to the body, antibodies, and immune cells can enter through disruption of the blood-brain barrier in neurodegenerative diseases, including PD (15). Experiments on rodent PD models have shown that in systemic inflammation, macrophages migrate into the cerebral tissue and transform into microglial cells, which are more present in the substantia nigra (16).

Immunity in Parkinson’s disease

Activation of lymphocytes leads to an increase in CD3+, CD4+, and CD8+ T cells in the substantia nigra, a reaction that causes neuronal damage. Activated immune cells can produce low levels of inflammatory mediators such as the cytokines IL-1β, IL-6, TNF (the receptor of this cytokine is more expressed in T cell patients), and other mediators that contribute to disease. These cytokines are released by activated microglial cells that occupy the substantia nigra and other brain areas involved in PD. Nitrogen monoxide, also called nitric oxide (NO), is an endogenous mediator of vascular processes involved in PD (17).

Activation of the innate immune system driven by microglia causes neuroinflammation, contributing to the death of neurons. The NLRP3 inflammasome signal in microglia is a complex that includes several proteins involved in the inflammatory process in PD. Microglia are similar to monocytes, and in PD, they have CD14 receptors activated, which causes them to increase in number and contribute to the inflammatory state (18). Elevated microbial infections with lipopolysaccharide-producing Gram-negative bacteria, which cause elevated type II interferon (IFN-γ) levels, can also lead to PD. CCL2 chemokines are activated in the disease and contribute to the recruitment of inflammatory monocytes. In addition, both CCL2 and CXCL8 chemokines are elevated in PD and contribute to the recruitment of the lymphocytic and neutrophil lineages, respectively (19). Therefore, dysfunctions of innate immune molecules may be contributing factors to PD.

In the brain of PD patients, in addition to circulating monocytes, activated CD3+, CD4+, CD8+, and Treg lymphocytes can also be found in the substantia nigra and contribute to the pathogenesis of the disease (20). This concept demonstrates that adaptive immunity also participates in brain damage.

In PD, there is a lower number of circulating CD4+ cells than in healthy subjects, while CD45RO+ memory cells are increased (21). This dysregulation is due to a deficiency in the neurotransmitter chemical messenger L-dopa. Regarding Treg cells, although conflicting results have been reported, it seems that dopamine deficiency leads to a lower reactivity of these T cells, a phenomenon correlated with the severity of the disease.

Dopamine receptors are different, ranging from D1 to D5, and are found to be highly expressed on B cells, memory T cells, and natural killer (NK) cells, while they are expressed in lower quantities by neutrophil granulocytes. It seems that the D3-type dopamine receptor is the one most associated with the pathological state of the disease (22). In PD, the CD95/CD3 ratio in lymphocytes is higher than in healthy subjects, and this appears to be linked to low levels of dopamine (23). In fact, after administration of L-Dopa, the CD95/CD3 ratio was found to be decreased (23). Levels of pro-inflammatory cytokines can also be reduced by dopamine administration, an effect that is mediated by microglia.

The number of dopamine receptors on T cells correlates with the severity of the disease. In fact, in PD, the T lymphocytes showing elevated levels of TNF receptors are more suppressed by this cytokine. Along with the inflammatory cytokine IFN-γ, this reaction increases with consequent immunosuppression and inflammation (Table II).

Table II. *Some of the over 50 immune, non-immune, and inflammatory biomarkers in PD.*

Inflammation factors:	IL-1β, TNF-α, IL-2, IL-6, IFN-γ, IL-15 (in serum), and other cytokines. NLRP3 inflammasome signal, TNFR1 (in serum), macrophage-migration Inhibitory Factor (MIF). Nitric oxide (NO).
Lymphocytes:	CD3+, CD4+, CD8+, CD95/CD3, NK cells, and others.
Chemokines:	RANTES, MCP-1 and MIP-1α (in PBMC supernatant), CCL2, and CXCL8 (IL-8)
Antibodies against different molecules and autoantibodies.	

Patients with PD have microglial cells with excess levels of MHC-II (24) and CD4+ and CD8+ lymphocytes, which is correlated with the severity of the disease and the death of neurons. These immune reactions lead to an increase of cytokines such as IL-1, TNF, IL-6, IFN-γ, and inflammatory IL-2 in cerebrospinal fluid (CSF), which induces pro-inflammatory IL-1 (even in an autocrine loop). Moreover, the increase in TNF is correlated with the degeneration of the substantia nigra and the worsening of the disease (25). Therefore, clinical therapies in PD focus on immune dysregulation and inflammation. The higher the pro-inflammatory cytokines and chemokines in the peripheral blood, the more severe PD is. Inflammation mediated by microglial cells is triggered by the activation of MAPK, JAK-STAT and NF-kB, which can be targeted for therapeutic effects.

CONCLUSIONS

In conclusion, in this report, we state that cytokines play a key role in PD, both as regulators of the immune system and as inflammatory molecules causing neurotoxicity, neuronal death, and neurodegeneration. The most widely used treatments today include L-Dopa, dopamine agonists, and anticholinergics. Recently, improvements have been made in the pharmacological therapies for PD, although specific treatments for this disease are still unknown.

Conflict of interest

The author declares that they have no conflict of interest.

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