INFLAMMATORY BOWEL DISEASE
Correlation Between Changes in the Gastrointestinal Microbiota with the Onset and Complications of Parkinson’s Disease: The Role of Inflammatory Cytokines in the Bidirectional Gut-Brain Axis

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Abstract
Humans developed a symbiotic relationship with their gut microbiota, a complex microbial community made up of bacteria, archaea, protists, and viruses, including bacteriophages. The enteric nervous system (SNE) is a gateway to bidirectional communication between the brain and the intestine, mainly through the Vagus Nerve (VN). Therefore, environmental exposure plays a fundamental role in both the composition and functionality of the intestinal microbiome and can contribute to susceptibility to neurodegenerative disorders, such as Parkinson’s disease (PD). This is a systematic review of the literature using the databases PUBMED, Scielo, and MEDLINE, using the descriptors present in the Health Sciences Descriptors (DeCS): Parkinson’s disease, cytokines, microbiota, and gastrointestinal tract. It can be mentioned that the neuropathological characteristic of PD is the generalized appearance of alpha-synuclein (α-Syn) aggregates in the central and peripheral nervous systems, including the SNE. Many studies suggest that intestinal toxins can induce the formation of α-Syn aggregates in the SNE, which can then be transmitted to the CNS via the VN. PD is strongly associated with aging and its negative effects on homeostatic mechanisms that protect against inflammation, oxidative stress, and protein malfunction. Thus, this study intends to carry out, based on analyzes of inflammatory cytokines and intestinal microbiota, how dysbiosis can contribute to the onset of complications of PD, promoting a correlation between clinical and laboratory manifestations and prognosis, as well as describing the main mechanisms of causal factors that are still poorly understood.

Keywords: Microbiota; Parkinson’s disease; Neurodegeneration; Inflammation; Cytokines.

Introduction
Parkinson’s Disease (PD) is a chronic progressive neurodegenerative disorder characterized by the early and prominent death of dopaminergic neurons in the compact part of the Substantia Nigra (SNpc) and the widespread presence of alpha-synuclein (α-Syn), a protein that acts at the level intracellular. In addition, dopamine deficiency in the basal ganglia leads to classic parkinsonian motor symptoms such as bradykinesia, tremor, rigidity, and posterior postural instability [1].

However, α-Syn is an Intrinsically Disordered Protein (IDP), without a stable 3D structure under physiological conditions and is characterized by exacerbated structural plasticity and conformational adaptability. Thus, like other IDPs, which have amyloidogenic regions, α-Syn can transform into a heterogeneous ligand leading to abnormal interactions and the development of PD [2]. It is believed that the neuropathological characteristic of PD is promoted by the presence of cytoplasmic...
inclusions, called Lewy Bodies (LB) or Lewy neurites, in SNpc neurons. LBs are mainly composed of α-Syn aggregates, whose aberrant soluble oligomeric conformations are mediated by their toxic effects [3].

PD is also associated with non-motor symptoms, which may precede motor symptoms by more than a decade, such as olfactory and gastrointestinal dysfunction. In this sense, it has been scientifically demonstrated that aggregates of α-Syn fibrils are also found in tissues located outside the Central Nervous System (CNS) of patients with PD, for example, in the autonomic nervous system and also in the Enteric Nervous System (ENS) [4].

Thus, it can be inferred that there is an intense bidirectional communication between the CNS and ENS through the intestine-brain axis, if occurs dysfunction along this communication base, it can lead the body to present severe problems, like the PD itself. It is also possible to mention that this orchestrated dialogue takes place through reciprocal connections that are mediated by the pelvic nerve, namely by the Vagus Nerve (VN). Therefore, VN turns out to be a good target for the use of neurostimulation therapies for the treatment of psychiatric and gastrointestinal disorders [5].

In this context, it is important to note that the gastrointestinal tract presents a complex microbial ecosystem, consisting of bacteria, archaea, protists, and viruses [6-8]. Thus, the human microbiome evolves with the host and maintains strict control over the intrinsic competitive nature of the microorganisms through the nervous and immune systems. This arrangement maximizes the benefits to the host, including protection against pathogens, improved nutrition, and mental health [1,5].

There is growing evidence of an association between microbiome dysfunction and CNS-related comorbidities such as anxiety, depression, autism spectrum disorders, Alzheimer’s, and Parkinson’s disease. This association likely arose as a by-product of the natural selection forces that act on microorganisms to adapt to the host and vice versa [7].

The effect of the microbiota on the CNS can lead to changes in the behavior of the individual associated with an increase in the aptitude of their bacterial populations. It is mentioned, for example, that the microbiota can influence social interactions, acting on the nutritional behavior of animals, particularly social species, where individuals share microorganisms and interact around the food. Furthermore, the neuroendocrinological and inflammatory mechanisms adjacent to this type of manipulation are widely shared by the host through its microbiome [6].

These factors generate a state of alert for the study of new targets of treatment for PD. Currently, the mainstay of PD management is pharmacological therapy; however, these symptomatic therapies have major limitations in advanced disease. Many disabling features develop later in the disease course, including non-motor symptoms, dopamine-resistant motor symptoms, and motor complications from long-term dopamine therapy. In addition, a large part of the pharmacological intervention does not take into account the microbial aspect installed in the individual and neither refers to the inflammatory process caused by a disarrangement of these microorganisms at the gastrointestinal level [9].

The aims of this study are to clarify some gaps that are not well described in PD, in addition to understanding how an inflammatory process at the gastrointestinal level, promoted by an alteration in the microbiota, can directly affect the intestine-brain bidirectional axis, emphasizing the role of inflammatory cytokines along this axis.

**Methodology**

This study is a systematic literature review, with a qualitative approach, considering the interpretation and analysis of the obtained elements [10]. The study’s guiding question was: “What is the relationship between PD and the intestine-brain bidirectional axis?”, following the steps: Identification of the theme, selection of the hypothesis or research question, establishment of inclusion and exclusion criteria, definition of the information to be extracted, evaluation of the studies included in the review, interpretation of results and presentation of the review with a synthesis of knowledge. The hypothesis established was: “The gut-brain axis, in synergy with dysbiosis and inflammatory cytokines, is directly involved in the etiology of PD”. The inclusion criteria defined for the selection of articles were: Articles that were available in full with online access in the researched databases, published in the period between the years 2008 to 2021. Exclusion criteria were the period, once that articles prior to 2008 were not selected, and gray literature, that is, material from literature not controlled by scientific or commercial editors.

The following databases were used: National Library of Medicine of the United States (PUBMED), Scientific Electronic Library Online (Scielo), Online Medical Literature Analysis and Retrieval System (MEDLINE), using the descriptors present in the Health Sciences Descriptors (DeCS) which are: Parkinson’s disease, cytokines, microbiota, and gastrointestinal tract. After this step, a discussion was held between the authors, resolving the differences through the re-reading of these publications, therefore, sixteen articles were selected.

**Parkinson’s disease overview**

Parkinsonism can be defined as a large category of diseases that may present a reduction in dopaminergic neurotransmission in the basal ganglia, which are classified as primary, secondary, plus, and heredodegenerative parkinsonism. This type of pathology is becoming more present in the world population, especially in individuals in an older age group [11].

It is known that PD affects about 1 to 2 people 1000 of the population, and the prevalence gradually increases with age, affecting about 1% of the population over 60 years of age. The main neuropathological finding of PD is Lewy bodies, which contain aggregates of α-synuclein-α-Syn, an intracellular protein. The cause of PD is unknown in most cases, but there is a strong relationship of genetic factors, including monogenic causes, in which, some genetic factors can be identified in 5-10% of patients. Furthermore, several other environmental factors are associated with an increased risk of PD [12,13].

This chronic progressive neurodegenerative disorder is characterized by the prominent early death of dopaminergic neurons in the pars compacta Substantia Nigra (SNpc) and the widespread presence of α-Syn. Thus, dopamine deficiency in the basal ganglia leads to classic parkinsonian motor symptoms such as bradykinesia, tremor, rigidity, and posterior postural instability [2].

**Current therapies**

PD is also associated with non-motor symptoms, which may precede motor symptoms by more than a decade. These
non-motor symptoms become bothersome symptoms in the later stages of PD. Currently, the mainstay of PD management is pharmacological therapy; however, these symptomatic therapies have major limitations in advanced disease. Many disabling features develop later in the disease course, including non-motor symptoms, dopamine-resistant motor symptoms, and motor complications from long-term dopamine therapy [4]. Although there have been remarkable advances in the medical and surgical treatment of PD, does not exist a definitive therapy for modifying the disease. However, new researches have been developed, it may be possible to identify new potential targets for the modification of the disease [6,14].

Gut-brain axis in the development of PD

Some studies relate the incidence of PD in Inflammatory Bowel Diseases (IBD), such as Crohn’s Disease (CD) and Ulcerative Colitis (UC). At this moment, five population-based cohorts have reported that the risk of PD is increased in patients with IBD, with a 20%-90% higher risk of developing PD than individuals without IBD [15]. However, the incidence of IBD among PD patients remains a topic of intense discussion, since the results are contrasting, for example, another study showed that PD patients had a 15% lower risk of developing CD and UC than non-PD controls [16].

In addition, it is important to note the monolayer of epithelial cells which separates the intestinal lumen and intestinal microbiome complex from the underlying lymphoid and enteric nerve tissues [1,14]. In this sense, microbial antigens can cross the intestinal epithelium through specialized cells, which can play a central role in localized inflammatory responses, and it is still possible to infer the participation of toll-like receptors in this process. These receptors are microorganism-sensitive proteins present in intestinal epithelial cells, mediating commensal bacteria recognition of harmful/inflammatory bacteria [8].

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New therapeutic targets

Moreover, some cytokines have been directly implicated in the pathogenesis of IBD in recent genetic and immunological studies, and appear to play a crucial role in inflammatory control. Studies of IBD in mouse models have shown that modulation of cytokine function can even be used for therapy. In addition, their main role is also relevant due to the fact that Tumor Necrosis Factor (TNF) blockade has been studied as an alternative treatment for IBD and, possibly, a future preventive therapy for PD [17].

It is notorious that some evidence shows that dysbiosis associated with the intestine and microbial components, generating inflammatory processes, are important agents and risk factors for PD. Consequently, the intestinal microbiome emerges as a potential target for protective measures aimed at preventing the onset of Parkinson’s disease [7].

Final considerations

PD is a neurodegenerative disease with multiple factors associated with the etiology. In this sense, the health of the intestine appears as a possible agent in the development of PD, with the intestinal microbiota having a fundamental role, once that studies show the relationship between bowel-associated dysbiosis and the components of the intestinal microbiota generating inflammatory processes, which, consequently, are risk factors for this disease.

Therefore, the protection of the intestinal microbiome presents as a potential alternative for the development of ways to protect and prevent PD. It is expected that from this research occurs an increase in knowledge about the risk factors of this disease, such as the participation of the bidirectional intestine-brain axis, in order to no only improve the forms of diagnosis and management of the PD, but also minimize the side effects arising from traditional treatment, improving the quality of life of affected individuals.

References


