v. 3, n. 70, 2023

International Journal of Health Science

HUMAN MICROBIOME: VILLAIN OR HERO?

Adriana Rocha Dal Lago Rodrigues
Universidade Cesumar. Maringá - Paraná, Brazil
https://orcid.org/0000-0002-3780-5481

Nicole Siqueira de Azevedo
Universidade Cesumar. Maringá - Paraná, Brazil
https://orcid.org/0009-0000-0715-6743

Valéria do Amaral
Universidade Cesumar. Maringá - Paraná, Brazil
https://orcid.org/0000-0002-6503-5269

All content in this magazine is licensed under a Creative Commons Attribution License. Attribution-Non-Commercial-Non-Derivatives 4.0 International (CC BY-NC-ND 4.0).

Abstract: Parkinson's disease (PD) is characterized by both motor and non-motor symptoms. Among the non-motor symptoms, alterations in the gastrointestinal tract are commonly found in patients with PD, which could serve as a causal link, or even premonitory symptoms of the disease. This literature review aimed to correlate the altered components in the gastrointestinal tract of patients with PD. Data search was based on guiding questions that answered which intestinal alterations can be observed in patients and what are their clinical manifestations; possible forms of screening were also investigated. From the search in databases such as: PubMed, ScienceDirect, Scielo and Web of Science, this integrative review was produced using Bardin's method (2011), PICo strategy, Boolean operators and PRISMA flow diagram. The study was double-blind and the articles used were published from Mar./2013 to Jul./2023, in Portuguese, English and Spanish, available for free. Results showed that changes in the gut microbiome were directly related to an increased permeability state, immune deficiency, and alpha-synuclein formation.
Keywords: Galt; tight joints; Microbiota; Alpha-synuclein; Lewy Bodies

INTRODUCTION

Parkinson's disease (PD) has clinical features divided into motor and non-motor symptoms. The motors and better known, are characterized by stiffness in the joints, difficulty in initiating movements and tremor at rest (POEWE et al., 2017). Among the non-motor symptoms are: sleep disorders, constipation and olfactory dysfunction - these being mainly related to the deposition of alpha synuclein in regions such as the olfactory bulb, upper brainstem, as well as regions of the peripheral autonomic nervous system (BORGHAMMER et al., 2022).

Alpha synuclein is a compound found naturally in presynaptic terminals, manifesting its pathogenic effect itself only when it is in a state of disorganized aggregation (URREA, 2018). The pathogenicity of alpha synuclein is directly related to oxidative stress - a tropism of these proteins with the mitochondrial compartments can be proven, which would culminate in a dysfunction in the electron transport chain, decrease in ATP production, generation of oxidative products and signaling of apoptosis pathways (ERUSTES, 2018). Studies indicate that dopaminergic neurons, because they have a more complex axonal network, demand greater mitochondrial activity, which makes them more prone to oxidative damage caused by the accumulation of alpha synuclein (GUIGUÉRI et al., 2019). In addition, the aggregation of alpha synuclein in neurons also promotes a decrease in the formation of dopamine-containing vesicles, which would culminate in a cytosolic accumulation of monoamines in the presynaptic terminal with the generation of oxidative products and eventual neuronal death (PIFL et al., 2014; GANAPATHY et al., 2016).

The pathogenicity of Parkinson's has been postulated to occur in 5 stages (Braak's stages) with symptoms being more noticeable at clinical levels in more advanced stages, when the degenerative process of melanoneurons located in the mesencephalic substantia nigra effectively occurs. A study promoted in Arizona aiming to correlate alpha synuclein findings with the clinical symptoms of patients with PD may confirm the segment order hypothesis proposed by Braak. In this, alpha synuclein aggregations were at first (STAGE 1) located in the olfactory bulb, predictably, these proteins proceeded to the medulla oblongata and pontine tegmentum (STAGE 2); in the next stage, motor symptoms become perceptible at clinical levels, with

clusters found in the substantia nigra and amygdala (STAGE 3); with the development of the pathology, there is an exacerbation of cognitive deficits with findings of alpha synuclein in regions of the temporal cortex (STAGES 4, 5) (ADLER et al., 2019). Braak and his colleagues, in addition to postulating the stages of progression of Parkinson's, also hypothesized how the onset of the disease would occur (Figure 1), in this case, the dysfunction and the clustering of alpha synuclein are initially found in peripheral regions, namely: nasal cavity and neurons of the enteric nervous system. From there, they would be transmitted in a standardized way to the central nervous system through the olfactory tract and/or the vagus nerve, respectively. This hypothesis is reinforced by the prodromal symptoms presented in PD patients - constipation, reduced sense of smell, nausea and dysphagia (BORGHAMMER et al., 2022). Several studies disagreed with the pattern of evolution proposed by Braak. However, an in vivo study based on the 18-year follow-up of a patient diagnosed with Parkinson's reported molecular findings and systemic manifestations arising in peripheral regions and continuing to the CNS, demonstrating that Braak's hypothesis, despite not being established in a standardized way in all cases, it remains a reliable parameter with regard to the evolution of the disease. (DONLON et al., 2021)

The gastrointestinal tract has mechanisms of protection against external antigens, at first mechanically, through the epithelium, but also immunologically through Peyer's patches, a cluster of lymphoid nodules located in the intestinal submucosal layer (ORIÁ et al., 2016). Gut-associated lymphoid tissue is responsible for capturing antigens and producing the humoral defense response primarily through the release of IgA, thereby reducing local inflammatory reactions and preventing systemic infections. Maintaining the integrity of the lymphoid system, as well as the physical barrier of the intestinal epithelium, depends on the composition of the individual's intestinal microbiota (BELLER R et al., 2020). The importance of intestinal immune defense is directly related to the peripheral formation of alpha synuclein, a nexus proven in vivo through research with animals infected by pathogenic bacteria, such as Enterobacteriaceae and Proteus mirabilis; after laboratory induction of infection, an increase in the formation of alpha synuclein can be seen in the intestine of the animals. (CHOI., et al., 2018; ORTIZ., et al., 2022). Strategies that avoid the formation of alpha synuclein in peripheral regions would therefore reduce the opportunity for their transmission to the CNS via the vagus nerve. after interruption of the vagus nerve, the animals showed a reduction in the pathognomonic motor and cognitive symptoms of the disease, reinforcing the intimate connection between the enteric nervous system - central nervous system axis and the modulations derived from this communication (KIM., et al., 2019)

To ensure the selective permeability of the intestinal epithelium, the production of a compound called mucin is associated with the epithelial protection mechanism, which has the ability to trap external pathogens and prevent their contact with the tight junctions of the epithelium (VOLYNETS et al., 2016). The effective production of mucin by the goblet cells takes place through a symbiotic association with the intestinal biome, specifically the Prevotella bacteria. States of intestinal dysbiosis with Prevotella spoils promoted a decrease in mucus production and an increase in intestinal permeability (SCHEPERJANS, 2014). Literature data also direct the symbiotic relationship of Prevotella with the production of ghrelin, a gastric compound responsible for the satiety

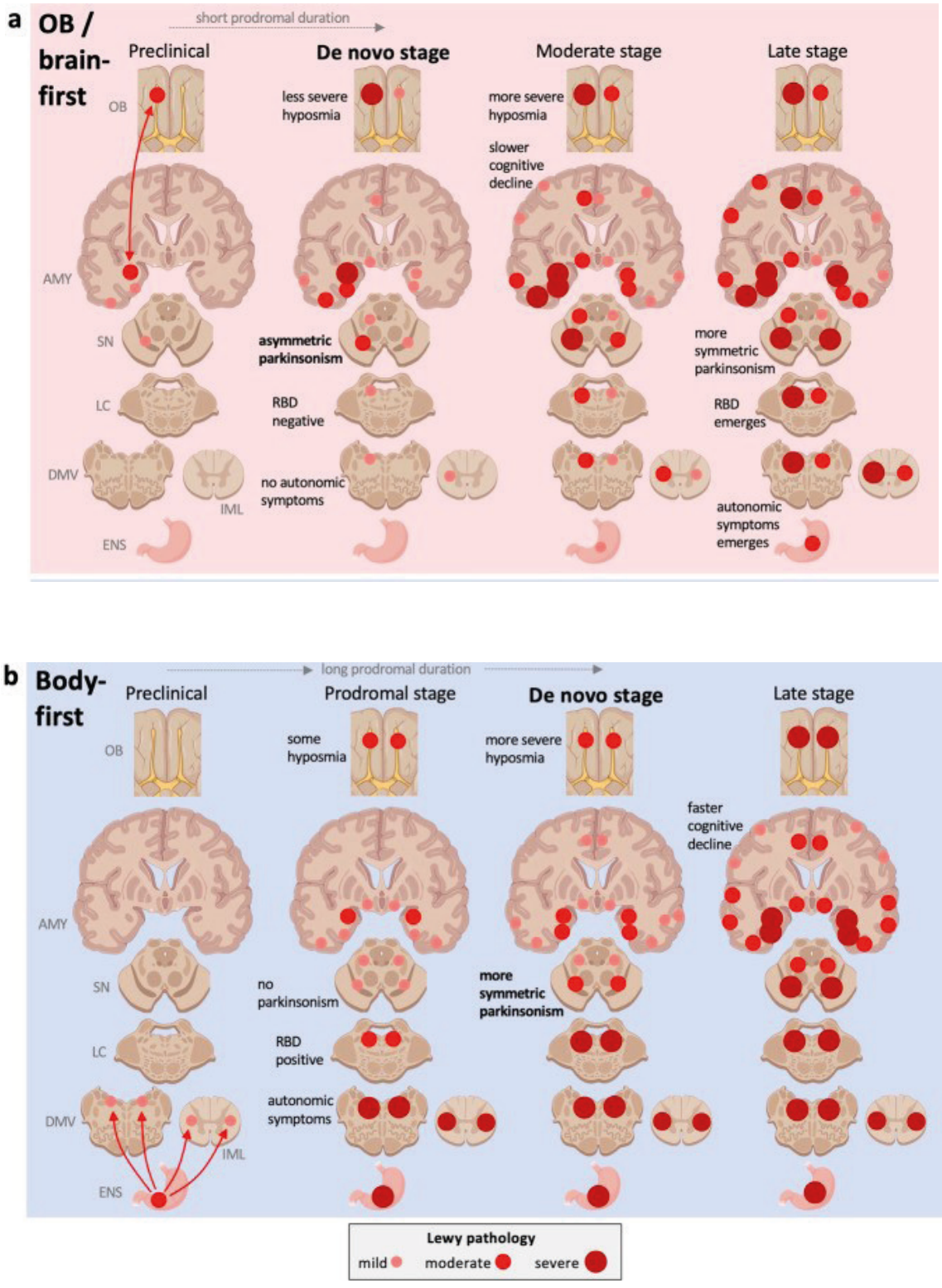

Figure 1- Hypothesis of single occurrence of prion-like propagation in Lewy body disorders (LBD).

Source: Borghammer., et al., 2022

response that communicates directly with the ventral tegmental area (KANG et al., 2016). The feeling of reward elicited in ATV through ghrelin occurs through the recruitment of dopaminergic neurons, therefore, its decrease would also be responsible for the reduction of the activation of these neurons (CORNEJO et al., 2018). In the literature, evidence can be found that patients with PD have a considerable decrease in Prevotella and Enterobacteriaceae bacteria (UNGER et al., 2016). It was also evident that the existence of a state of intestinal dysbiosis within Parkinson's disease with a decrease in Enterobacteriaceae was related to more exacerbated motor symptoms (SCHERPERJANS et al., 2014). Such studies demonstrate, therefore, that the composition of the intestinal microbiota can influence both the installation and the symptomatological manifestations of PD (SCHERPERJANS et al., 2014).

While the microbiome differentiates during the onset of Parkinson's, the amount of neuropeptides such as: CCK, BDNF, and Dyn A also becomes reduced (CHOI et al., 2021). Such molecules act analogously to neurotransmitters and are responsible for communicating peripheral events to the central nervous system; CCK can be widely found in the dendritic regions of dopaminergic neurons and acts as a negative feedback on dopamine release, its decrease, therefore, would lead to exacerbated release of dopamine in presynaptic terminals culminating in depletion and downregulation of the number of dopaminergic receptors (HAMAMAH et al., 2023). The decrease in Dyn A correlated with more evident motor deficits, as well as greater dopaminergic neuronal degeneration (CHOI et al., 2021). The relevance of the impact promoted within PD with the decrease of the BDNF neuropeptide is related to its ability to regenerate neuronal tissues. It can be seen that its synthesis is maintained in a balanced way through the symbiotic relationship with Bifidobacterium bacteria; rats that received supplementation of these bacteria showed an increase in hippocampal production of BDNF and consequently greater neurogenesis; therefore, the spoilage of such bacteria can be associated with the vulnerability of the outbreak of neurodegenerative diseases (AMAGASE, 2023). It is hypothesized in view of the findings that the alterations found in the prodromal period of the onset of Parkinson's disease, as they are subject to quantification, could serve as a form of screening in patients who have different symptoms and not explained by another condition, thus helping in the early diagnosis.

Given the proven relationship of changes in the intestinal microbiome within the pathogenicity of Parkinson's disease, new therapeutic approaches began to be considered. Such approaches aim to reduce alpha-synuclein aggregation in peripheral regions, as well as to promote increased neurorestoration mainly through the reversal of intestinal dysbiosis (SANCANDI et al., 2023). Dietary interventions aimed at maintaining a balanced pool of intestinal bacteria, associated with the drug treatment already recommended for Parkinson's disease, were proven to have a beneficial effect during an in vivo study, with an improvement in motor deficits (SULTHANA et al., 2023). In addition to improving already established deficits, anti-inflammatory diets and antioxidants based on natural products have also shown the potential to reduce the risk of PD outbreak (KALAMPOKINI et al., 2019). On the other hand, however following the same precept, diets rich in casein, an antigenic compound found in dairy products, exacerbate the symptoms of PD - such exacerbation was mainly associated with the increase in intestinal inflammation derived from the imbalance in the intestinal microbiota that

compounds with casein cause (PU et al., 2023). The protection generated through a balanced microbiota can be proven in vivo through the monitoring of parkinsonian patients who received a fecal microbiota transplant from healthy patients. of sleep, reinforcing the importance of a balanced intestinal biome in preventing damage to the GIT epithelium and consequent systemic inflammation followed by neuroinflammation (XUE, 2020).

The modulation of the symptomatological expression in Parkinson's disease from the regulation of the intestinal microbiota was also considered from the supplementation of probiotics. A randomized clinical study was guided by the administration of a probiotic compound containing Lactobacillus Acidophillus, Bifidobacterium bifidus, Lactobacillus reuteris and Lactobacillus fermentum in parkinsonian patients with subsequent analysis of the changes found in the MDS-UPDRS scale (a scale that organizes motor and non-motor symptoms of everyday life of patients with Parkinson's). After 12 weeks, patients who received the probiotic compound showed a decrease in the MDS-UPDRS score when compared to those in the placebo group, demonstrating a beneficial effect of probiotic supplementation in reducing PD symptoms (TAMTAJI, 2019). Another research outlined the proposed administration of a probiotic containing Lacticaseibacillus paracasei strain Shirota for a period of 12 weeks. At the end of the study, when compared to the placebo group, patients who received the probiotic compound reported improvement in non-motor symptoms of PD, highlighting - constipation, anxiety and depression (YANG, 2022). Pre-clinical or clinical evidence on the beneficial effects of probiotics on PD is still limited, but there are positive potentials in their adoption; given that the therapy has demonstrated the ability to restore the microbiota, support epithelial integrity and maintain immune homeostasis (WANG et al., 2018)

METHODOLOGY

An integrative review was carried out, through a literary survey of a descriptive nature over the last ten years (March 2013 to July 2023), of studies that show the relationship between dysbiosis and the development of PD. The selection of articles was carried out in a double-blind manner and the Bardin method (2011) and the PICo strategy, an acronym that represents non-clinical criteria for planning a research, were used to categorize the articles: "patient/population/problem " (P), "interest" (I), "context" (Co). The Boolean operators AND and OR were used to cross data from the descriptors, the checklist and the PRISMA flow diagram (Figure 1) were also used for the organization and eligibility of the articles.

As inclusion criteria, articles that answered the guiding questions "What is the relevance of dysbiosis in Parkinson's disease? How to choose screening, prevention and treatment systems for patients who have this dysbiosis?", in Portuguese, Spanish and English that they were freely available in the databases for reading. For the eligibility of the articles, articles published in full were considered, not just abstracts, in vivo, in vitro studies. For the execution of this project, a survey was carried out in databases, such as: PubMed, Oxford Academic, Nature Review Neurology, MDPI, Scielo, ScienceDirect and Web of Science.

The search for articles was based on Health Sciences Descriptors (DeCS) in Portuguese: enteric nervous system (ENS), Parkinson's disease, microbiota-intestinal-brain axis and combination of Boolean operators: enteric nervous system AND Parkinson's disease. For the selection of articles, the titles and abstracts were carefully read and, if considered relevant to the study, a complete interpretative reading of the study was carried out. Literature

reviews, articles published before 2012, articles that were not freely available, articles in which the reading of the abstract did not fit the guiding questions, articles in languages other than Portuguese, English and Spanish were excluded.

RESULTS AND DISCUSSION

In the first search carried out in the databases using the descriptors in the Portuguese language: enteric nervous system, Parkinson's disease, dysbiosis, microbiota-intestinal-brain axis in combination with the Boolean operators "AND" and "OR", 152,267 articles were found. From this initial total, 636 articles were selected that met the first selection phase, which was based only on reading the title and on the possibility of the article answering the guiding questions of the review. In the second phase of article selection, the authors then read the abstract and selected those that were related to the theme of the baseline research, resulting in 118 studies. During the third phase the inclusion and exclusion criteria were used resulting in a total number of 60 articles. These studies were relevant to the overall understanding of the researched topic. However, the authors chose 7 works that were able to answer all the guiding questions, within the last 10 years. Figure 2 demonstrates all selection and eligibility stages of the articles consulted for the production of the integrative review.

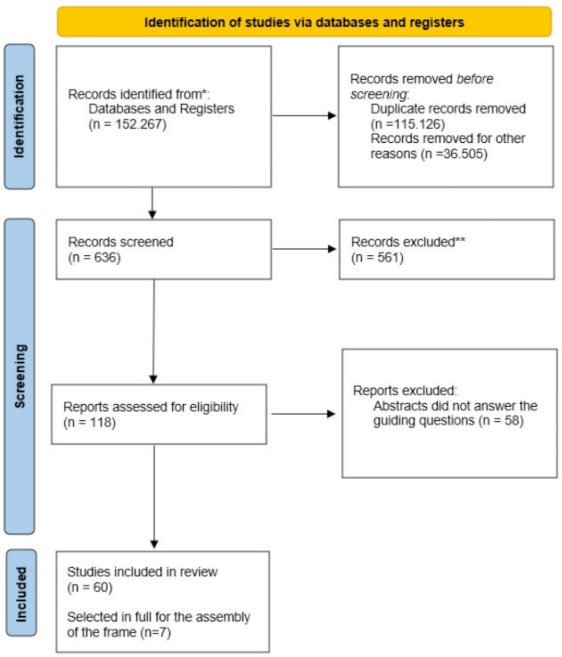

Figure 2. Flowchart of the integrative review article selection phases;

Source: adapted from Page et al., 2021

Among the articles grouped in the third phase (n=60), 81.6% (n=49) were published in English, 15% (n=9) in Portuguese and 3.4% (n=2) in Portuguese. Spanish. Since 75% (n=45) were published in the PubMed database and 25% (n=15) in other databases that separately did not reach the percentage of 6%. Based on the analysis of the types of methodological approaches found in the works, 21 (35%) in vivo studies in animals were carried out, among which 17 (80.9%) used mice, 3 (14.2%) used rats and 1 (4.9%) was developed in pigs. There were also 5 (8.3%) in vitro studies, 20 (33.3%) studies in the experimental phase with humans and the others, 11 (18.3%) were bibliographical reviews and 3 (5.1%) were from specific literature in the area. Published for several years, with few publications in 2013 and more robust and research-intensive publications in the years 2022 and 2023.

The studies by Borghammer et al. (2022) were based on the collection of data from 320

patients, in the Vantaa and Tokyo networks, about immunohistochemical data and parameters of alpha synuclein clusters found in the postmortem of patients with PD. The authors subdivided the sample into 3 paired groups according to the clinical presentations that they demonstrated in life. The results of the research demonstrated a relationship between milder clinical symptoms, with agglomerations of alpha synuclein contained in the olfactory bulb or ENS (Enteric Nervous System), while more severe clinical symptoms correlated with agglomerations of alpha synuclein in regions such as: brainstem and regions cortical. Using another approach, Donlon et al. (2021), in an in vivo study, followed a patient for a decade who presented peripheral sensory deficit as an initial symptom. During this period, the patient presented worsening of the neuropathy and progression to autonomic symptoms, when he was diagnosed with PD. A retrospective analysis of a biopsy of the sural nerve, performed for another reason at the beginning of the investigations, showed that premonitory to the classic symptoms of PD, the patient had inclusions of alpha synuclein in nerves in the peripheral region. Demonstrating a pattern in the development of PD with deficits occurring at first in peripheral regions of the nervous system.

Scheperjans et al. 2014, compared the composition of the intestinal microbiome of 72 patients with PD and 72 patients without the disease (control group). At the end of the study, the authors concluded that outside the control group there was a reduction in Prevotella bacteria, concomitant with an increase in intestinal permeability. Still on the intestinal epithelial dysfunction found in Parkinson's disease, Devos et al. (2013) tested the hypothesis that PD patients have an exacerbated intestinal inflammatory state. For this purpose, the authors performed a biopsy of the ascending colon of patients with PD and patients in a control group without Parkinson's. PCR quantifications indicated an increase in inflammatory cytokines in the group with Parkinson's, supporting the researchers' initial hypothesis. From another point of view, but still dealing with the altered components in the intestinal tract of parkinsonian patients, Sancandi et al. (2023) analyzed the effects of administering probiotics in Wistar rats with PD. The animals were separated into groups, one group treated with probiotic and the other without treatment. Histological analysis, post mortem of enteric tissue samples, showed that the group that received the probiotic showed a decrease in neuroinflammatory markers and protection of intestinal epithelial integrity. Such studies show, therefore, the existence of intestinal alterations occurring within the follow-up of neurodegenerative diseases. Pu et al. (2023), through the analysis of mice with induced PD, investigated the relationship between the consumption of dairy products with the worsening of the clinical presentation of the disease, their results demonstrated that the mice exposed to casein had reduced motor coordination and reduced the general content of dopamine, concomitant with an increase in intestinal inflammation. The findings therefore indicate that alterations in the intestinal biome are likely to modulate the clinical presentations of PD.

Tamtaji et al. (2019) through a double-blind randomized clinical study with 60 patients with PD, evaluated the influence of probiotic supplementation containing Lactobacillus acidophilus, Bifidobacterium bifidum and Lactobacillus fermentum over 12 weeks, the study patients were divided into groups that received placebo and groups that received the probiotic; in the results phase, the group that received the probiotic showed improvement in clinical symptoms based on the MDS-UPDRS classification, a scale,

which according to Skorvanek et al. (2017), analyzes motor and non-motor symptoms of PD and correlates them with the stages of disease progression. It can be inferred, given these studies, the relevance of the intestinal biome in the perpetuation of deficits derived from PD. The studies by Sulthana et al. (2023) also evaluated the impact of changes in the intestinal microbiome on the clinical symptomatology of Parkinson's, therefore, the authors followed a 54-year-old female patient for 2 months while she received targeted dietary intervention, containing food groups named by the researchers as: super vegetables, super fruits, whole grains, spices and animal protein; at the end of the study, an improvement in the patient's motor capacity could be observed, using the Hoehn and Yahr scale as a parameter. Supporting, therefore, the hypothesis of the possibility of improvement in symptoms in PD through the modulation of the intestinal biome.

Another research idealized by Xue et al. (2020) with fecal microbiota transplantation elected 15 patients with PD, dividing them into 2 groups, with group 1 consisting of 10 patients who received transplantation by colonoscopy and group 2 containing 5 patients who received transplantation via naso-intestinal. The authors observed improvement in the clinical symptoms of patients, based on the PSQI scales (assess sleep quality, HAMD (assess depression symptoms), HAMA (assess anxiety symptoms), PDQ-39 (quality of life) and UPDRS-III (motor symptoms) According to the results found by the authors, it can be concluded that actions aimed at improving the intestinal microbiota beneficially influence several aspects included in the clinical presentation of PD.

Choi et al. (2021) performed the dosage and quantification of neuropeptides in healthy rats and rats with laboratory-induced PD. The authors used PCR and Western Blot to investigate the intestinal neuropeptides found in the animals and demonstrated that the animals with PD showed a decrease in CCK, BDNF, Dyn A and neurotrophin. Thus, demonstrating a possible form of screening in the population. Furthermore, Hamamah et al. (2023) investigated the correlation between CCK and dopamine concentrations. For this purpose, the authors used different groups of samples, with group 1 Otsuka Long-Evans Tokushima Fatty (OLETF) (genetically modified mice showing deficiency in CCK receptors) and group 2, without deficiency. The research evidenced, through the analysis of autoradiography, that the animals with deficiency in the receptors presented greater release of dopamine when nourished with sugary foods. Denoting that there is a regulatory mechanism, on the part of CCK, in the activity of dopaminergic neurons and their role within the progression of PD.

According to Izumi et al. (2014) the accumulation of dopamine in the cytosolic region leads to oxidative damage and subsequent cell death. Cultures of midbrain and adrenal cells extracted from rats were exposed to an herbicidal compound (Paraquat) capable of increasing intracellular dopamine content. The results showed that the accumulation of dopamine in the cytosolic region leads to oxidative damage and subsequent cell death, thus validating the assumption. Still within the investigation of the possible degenerative mechanisms found in PD, the study carried out by Pifl et al. (2014) analyzed brain tissues removed in the postmortem period of patients diagnosed with PD. The research was based on comparing the amount of dopamine in the cytosolic region found in the brain tissues of patients with PD with those of a control group without the pathology. At the end of the investigation, the authors found that the group with PD had a significant increase in dopamine in the cytosolic region. This finding

was related during the research with the reduction in the number of amine transporter vesicles, denoting that the cytosolic increase of DA could be provoked from defects in these transporters. Given these results, it is evident that within the pathogenicity of PD changes in several pathways corroborate with the exhaustion and death of dopaminergic neurons.

The authors Guigueri et al. (2019) investigated the influence of the structure of dopaminergic neurons on the vulnerability of PD, the authors performed in vivo measurements in rats of the axonal processes of these animals in specific regions such as the ventral tegmental area and the substantia nigra, and demonstrated that the neurons of the substantia nigra have larger axonal extensions, greater mitochondrial activity and, therefore, would be more susceptible to oxidative damage. Erustes (2018), through the analysis of cell cultures, demonstrated that alpha synuclein has tropism for mitochondrial membranes, which would lead to a decrease in ATP production and signaling to apoptosis pathways. Combining the knowledge of the authors, it is understood that the clinical presentation found in Parkinson's disease is related to the fragility of the dopaminergic pathways in face of systemic alterations.

CONCLUSION

After collecting data on intestinal dysbiosis and its relationship with Parkinson's disease, we can highlight that the gut-brain axis is an important target in screening planning, taking into consideration, the composition of neuropeptides and proportion of intestinal bacteria, as well as a symbiotic pathway that must be considered when choosing the treatment of the disease.

REFERENCES

ADLER, Charles H. et al. **Unified staging system for Lewy body disorders: clinicopathologic correlations and comparison to Braak staging.** Journal of Neuropathology & Experimental Neurology, v. 78, n. 10, p. 891-899, 2019.

BELLER, Alexander et al. **Specific microbiota enhances intestinal IgA levels by inducing TGF-β in T follicular helper cells of Peyer's patches in mice.** European journal of immunology, v. 50, n. 6, p. 783-794, 2020.

CHOI, Jin Gyu et al. **Reduced levels of intestinal neuropeptides and neurotrophins in neurotoxin-induced parkinson disease mouse models.** Journal of Neuropathology & Experimental Neurology, v. 80, n. 1, p. 15-20, 2021.

CHOI, Jin Gyu et al. **Oral administration of Proteus mirabilis damages dopaminergic neurons and motor functions in mice.** Scientific reports, v. 8, n. 1, p. 1275, 2018.

DEVOS, David et al. **Colonic inflammation in Parkinson's disease.** Neurobiology of disease, v. 50, p. 42-48, 2013.

DONLON, Eoghan et al. Braak's Unfinished Hypothesis: **A Clinicopathological Case Report of α-Synuclein Peripheral Neuropathy Preceding Parkinsonism by 20 Years.** Movement Disorders Clinical Practice**,** v. 8, n. 7, p. 1129-1133, 2021.

ERUSTES, Adolfo Garcia. **Desenvolvimento, Caracterização E Estudos Da Autofagia E Apoptose Em Modelo Celular De Doença De Parkinson**. 2018.

GANAPATHY, Kavina et al. **Influence of 6-Hydroxydopamine Toxicity on α-Synuclein Phosphorylation, Resting Vesicle Expression, and Vesicular Dopamine Release.** Journal of Cellular Biochemistry**,** v. 117, n. 12, p. 2719-2736, 2016.

GIGUÈRE, Nicolas et al. **Increased vulnerability of nigral dopamine neurons after expansion of their axonal arborization size through D2 dopamine receptor conditional knockout.** PLoS genetics, v. 15, n. 8, p. e1008352, 2019

HAMAMAH, Sevag; HAJNAL, Andras; COVASA, Mihai. **Reduced Striatal Dopamine Transporter Availability and Heightened Response to Natural and Pharmacological Stimulation in CCK-1R-Deficient Obese Rats.** International Journal of Molecular Sciences, v. 24, n. 11, p. 9773, 2023.

IZUMI, Yasuhiko et al. **Endogenous dopamine is involved in the herbicide paraquat-induced dopaminergic cell death.** Toxicological Sciences, v. 139, n. 2, p. 466-478, 2014.

KALAMPOKINI, Stefania et al. **Nonpharmacological modulation of chronic inflammation in Parkinson's disease: Role of diet interventions.** Parkinson's Disease, v. 2019, 2019.

KANG, Chao et al. **Healthy subjects differentially respond to dietary capsaicin correlating with specific gut enterotypes.** The Journal of Clinical Endocrinology & Metabolism, v. 101, n. 12, p. 4681-4689, 2016.

KIM, Sangjune et al. **Transneuronal propagation of pathologic α-synuclein from the gut to the brain models Parkinson's disease.** Neuron, v. 103, n. 4, p. 627-641. e7, 2019.

ORIÁ, Reinaldo Barreto; BRITO, GA de C. **Sistema digestório: integração básico-clínica.** Editora Edgard Blucher Ltda, 2016.

MINATO, Tomomi et al. **Progression of Parkinson's disease is associated with gut dysbiosis: two-year follow-up study.** PloS one, v. 12, n. 11, p. e0187307, 2017.

ORTIZ DE ORA, Lizett; UYEDA, Kylie S.; BESS, Elizabeth. **Discovery of a Gut Bacterial Metabolic Pathway that Drives α-Synuclein Aggregation and Neurodegeneration.** bioRxiv, p. 2022.06. 08.495350, 2022.

PIFL, Christian et al. **Is Parkinson's disease a vesicular dopamine storage disorder? Evidence from a study in isolated synaptic vesicles of human and nonhuman primate striatum**. Journal of Neuroscience, v. 34, n. 24, p. 8210-8218, 2014.

POEWE, Werner et al. **Parkinson disease (Primer)**. Nature Reviews: Disease Primers, v. 3, n. 1, 2017.

PU, Zhengjia et al. **Casein Reactivates Dopaminergic Nerve Injury and Intestinal Inflammation with Disturbing Intestinal Microflora and Fecal Metabolites in a Convalescent Parkinson's Disease Mouse Model**. Neuroscience, 2023.

ROCHA, Priscilla; BARROS, Maria EG; EVÊNCIO-NETO, Joaquim. **Análise morfométrica da parede intestinal e dinâmica de mucinas secretadas no jejuno de frangos suplementados com probiótico Bacillus subtilis cepa C3102.** Pesquisa Veterinária Brasileira, v. 36, p. 312-316, 2016.

SANCANDI, Marco et al. **Effects of a probiotic suspension Symprove™ on a rat early-stage Parkinson's disease model.** Frontiers in Aging Neuroscience, v. 14, p. 1525, 2023.

SCHEPERJANS, Filip et al. **Gut microbiota are related to Parkinson's disease and clinical phenotype**. Movement Disorders, v. 30, n. 3, p. 350-358, 2015.

SKORVANEK, Matej et al. **Relationship between the MDS-UPDRS and quality of life: a large multicenter study of 3206 patients.** Parkinsonism & related disorders, v. 52, p. 83-89, 2018.

SULTHANA, Ayesha et al. **Gut microbiome-based dietary intervention in Parkinson disease subject: A case report.** International Journal of Nutrition, Pharmacology, Neurological Diseases, v. 13, n. 3, p. 158-165, 2023.

TAMTAJI, Omid Reza et al. **Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial.** Clinical Nutrition, v. 38, n. 3, p. 1031-1035, 2019.

UNGER, Marcus M. et al. **Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls.** Parkinsonism & related disorders, v. 32, p. 66-72, 2016

URREA ZAZURCA, Laura et al. **Funciones de la proteína priónica celular, alfa-sinucleína y reelina en enfermedades neurodegenerativas.** 2018.

VOLYNETS, Valentina et al. **Intestinal barrier analysis by assessment of mucins, tight junctions, and α-defensins in healthy C57BL/6J and BALB/cJ mice**. Tissue Barriers, v. 4, n. 3, p. e1208468, 2016.

WANG, Jing et al. **Probiotic Lactobacillus plantarum promotes intestinal barrier function by strengthening the epithelium and modulating gut microbiota**. Frontiers in microbiology, v. 9, p. 1953, 2018.

XUE, Liu-Jun et al. **Fecal microbiota transplantation therapy for Parkinson's disease: a preliminary study.** Medicine, v. 99, n. 35, 2020.

YANG, Tao et al. **Gut dysbiosis is linked to hypertension.** hypertension, v. 65, n. 6, p. 1331-1340, 2015.

YANG, Xiaodong et al. **Effect of Lacticaseibacillus Paracasei Strain Shirota Supplementation on Clinical Responses, Gut Microbiota and Faecal Metabolites in Patients with Parkinson's Disease: A Randomized, Double-Blind, Placebo-Controlled Trial**. Lacticaseibacillus Paracasei, 2022.