UNIVERSITY OF MEDICINE AND PHARMACY

"CAROL DAVILA" BUCHAREST

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MEDICINE

PHD THESIS

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PhD student: DĂNĂU ADELA

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INFLUENCE OF GUT MICROBIOTA ON THERAPEUTIC RESPONSE IN PATIENTS WITH ADVANCED PARKINSON'S DISEASE

ABSTRACT OF PHD THESIS

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Parkinson's disease (PD), one of the most common neurodegenerative diseases, affects approximately 1% of the population over 60 years of age, with peak incidence in people aged 70-79 years and in males [1]. Its prevalence is increasing as the population ages [18]. It causes progressive disability with major functional, social and economic impact. There is currently no cure or treatment to slow the progression of PD.

Predominantly sporadic, PD has a multifactorial, incompletely understood etiopathogenesis. Multiple complex and interconnected mechanisms are the subject of current research to better integrate them for the development of disease-modifying therapies. Alpha-synuclein (AS) misfolding, mitochondrial dysfunction, inflammatory mechanisms and oxidative stress are just a few [1]. In addition to the involvement of dopaminergic pathways, glutamatergic, serotonergic and adrenergic pathways are being explored as alternatives to identify biomarkers and therapeutic solutions. Currently, selective damage to dopaminergic neurons in the substantia nigra (pars compacta) with degeneration of the nigrostriatal tract is considered an absolutely necessary feature for diagnosis, being also the alteration that determines progressive motor disability. The name "substantia nigra" comes from the dark colour of the neurons, due to the accumulation of a pigment called neuromelanin, which is visibly reduced in a post-mortem analysis of the brains of people with PD [2]. The pattern of neuronal loss in PD is distinct/different from that in the ageing process, which occurs relatively uniformly, not with selectivity for areas of the substantia nigra. Neuronal death is retrograde, from periphery to centre. Braak et al., after post-mortem study of the brains of PD patients, proposed that the sporadic variant of the disease is the result of a combination of genetic and environmental factors, and that the occurrence of PD has a mechanism reminiscent of a pathogen entering the body via the nasal cavity, being swallowed and triggering misfolding of alpha-synuclein and production of Lewy bodies in the enteric nervous system; propagation from this level to the brain is via the vagus nerve in a prion-like manner [3,4]. Most of the recent studies provided evidence supporting this hypothesis [5].

The cardinal clinical manifestation for PD is parkinsonian syndrome (defined, according to MDS 2015 criteria, as bradykinesia accompanied by rest tremor and/or rigidity) [24]. Parkinsonian syndrome is the expression of selective degeneration of dopaminergic neurons in the mesencephalic substantia nigra, with consequent reduction in the amount of dopamine released in the striatum [13,14]. The diagnosis of certainty is histopathological, the sine qua non being the presence of intraneuronal aggregates of conformationally altered AS, called Lewy bodies [15].

Significant improvement of the parkinsonian syndrome upon levodopa administration is mandatory for the clinical diagnosis of PD. Among the non-motor manifestations of PD a central place is occupied by intestinal motility disorder, constipation being the first symptom of the disease in up to two thirds of people with PD.

PD became a medically defined and recognised entity in 1817, following a famous medical publication by the London physician James Parkinson. The publication was based on his own findings after researching 6 cases with similar symptoms [41,42].

Over the last decades, the epidemiological profile of neurological pathologies has changed in high-income countries (Western Europe and North America), with a decrease in the number of cases of ischemic stroke, while reports of PD, Alzheimer's disease and amyotrophic lateral sclerosis are increasing [18].

The information used came from data stored in the Global Burden of Disease, Injuries, and Risk Factors (GBD), showing that the number of PD cases has doubled in the last 26 years, from 2.5 million to over 6 million. If true, this represents a major public health problem with major social and economic impact. It is important to note that this doubling of reporting has certainly been contributed to by the increase in life expectancy, changes in environmental factors (urbanisation, pollution, industrialisation, population migration), changes in the flow of information in terms of diagnostic accuracy and the standardisation of diagnosis developed over the years [18, 34, 35, 36, 37].

The etiopathogenesis of PD is multifactorial and not fully understood. Most recent studies show that in both monogenic and sporadic forms of PD, misfolding AS with subsequent aggregate formation (such as Lewy bodies in PD and Lewy body disease) and prion-like trans-synaptic propagation of the pathology is a central etiopathogenic event - thus, certain changes in AS may serve as both biomarkers and potential therapeutic targets [7, 16, 17].

The gut microbiome constitutes a complex ecosystem of bacteria, viruses, fungi and archaea (and until recently, i.e. still valid for some geographical regions, also parasites), which recently, thanks to molecular analysis techniques, could be mapped to identify the thousands of species present locally and their interactions under physiological and pathological conditions. The link between the enteric and the central nervous system has raised increased interest in modifying the evolution of diseases in preclinical stages, but also in therapeutic options, which tend to have a more than symptomatic role. The gut microbiome plays a role in producing and facilitating the

absorption of certain nutrients and pharmacological formulations, with the possibility of modulation/adaptation/modification in relation to environmental factors [31, 32].

The gut-brain axis is a complex system of interconnected mechanisms through which bidirectional communication between the gastrointestinal tract and the brain takes place, with the participation of the immune system, the neuroendocrine system, the hypothalamic-pituitary-adrenal (HPA) axis, the vagus nerve, the autonomic system through sympathetic and parasympathetic connections, the enteric nervous system and the gut microbiome. Studies in recent years have mainly focused on substances with neuroactive properties produced by the gut microbiota and how they influence or even cause certain central nervous system (CNS) pathologies [87]. Recent data point to inflammation and altered permeability of the gut mucosa as a possible precursor to PD. Although there is a diversity of up to 1000 different species, the 4 major families - Bacteroides, Firmicutes, Actinobacteria and Proteobacteria - are predominant [92]. Under normal physiological conditions, they participate in digestion, absorption, angiogenesis, development and maintenance of an optimal immune system, providing protection against pathogens. Lactobaccillus, Enterococcus, Bifidobacteria and Steptococcus are bacteria involved in the production of major neurotransmitters such as gamma-aminobutyric acid (GABA) and acetylcholine. Interestingly, the serotonergic circuit signals are transmitted, given that 90% of serotonin is produced in the gut microbiome and tryptophan metabolised in the gut is involved in microglial activation and protein transcription in astrocytes, thereby modulating the inflammatory response in the brain. The action of tryptophan on microglia has also recently been linked to the release of a neurotoxin, quinolinic acid, which is also implicated in the pathogenesis of Huntington's disease and depression [93].

The gut microbiome differs significantly in people with PD compared to healthy people. Local gut changes are correlated with systemic immune response, frequently with the production of an excess amount of pro-inflammatory markers.

Systemic and peripheral inflammation are involved in the pathogenesis and progression of PD [88, 89]. This correlation was initially observed in the development of a parkinsonian syndrome in post -viral contexts (influenza, herpesvirus, varicella-zoster, etc). Although these are physiological processes designed to provide protection against pathological agents, they may initiate or promote exaggerated response mechanisms with damaging effects. Chronic

inflammation is considered to be a contributor to disease progression, but also to the maintenance of neuroinflammatory status.

Individual genetic profile, environmental factors, diet are all factors that determine each microbiome to have its own structural and functional particularities. There are considerable differences between the microbiota of healthy individuals versus those with PD, as demonstrated by laboratory studies [94, 95, 96].

Gastrointestinal disorders associated with PD are thought to be mainly the consequence of damage to the enteric and autonomic nervous systems; they can occur at any level of the gastrointestinal tract and are present in approximately 60-80% of people with PD (a statistic demonstrated by cohort and necropsy studies). Communication between the gut microbiota and the brain is based on Braak's theory. According to it, a pathogen is involved in the aetiopathogenesis of PD that penetrates through the nasal mucosa, reaches the gut, where it causes conformational changes in the AS and is then transmitted upwards through the vagus nerve route to the brain [3,100]. Gastrointestinal disorders associated with PD may precede the motor stage, or may manifest during its progression, contributing to impaired quality of life. Gastrointestinal symptoms range from salivary disorders that can affect the dentition by altering oral ph, to false hypersalivation which is the accumulation of saliva through swallowing disorders, oesophageal disorders, pharyngeal disorders, gastroparesis (nausea, loss of appetite, bloating), Helicobacter pylori (HP) infection, intestinal dysmotility, small bowel bacterial overgrowth syndrome, micturition disorders and anorectal dysfunction. All of these contribute significant additional disability to the motor picture, which affects quality of life, but more importantly can be life-threatening; aspiration pneumonia is a severe, potentially life-threatening complication through acute respiratory failure or other complications.

Small intestinal bacterial overgrowth (SIBO) is an intestinal dysbiosis that occurs in people with predisposing factors (e.g. chronic intestinal hypomotility/slowing of intestinal transit, anatomical changes of the intestinal tract, hypochlorhydria). Although not a disease, it may be associated with bowel symptoms (abdominal discomfort, bloating), typically relieved after antibiotic treatment [154, 155]. In PD, SIBO is related to non-motor symptoms and motor complications due to gastrointestinal mucosal changes through the development of low-grade inflammation with cellular degeneration, including oxidative stress.

The association between SIBO and PD was recently demonstrated by Xiaqing Li et al. who conducted a review of the literature published up to February 2021 on this topic. The meta-analysis documented the connection between the two conditions, with small bowel bacterial overgrowth syndrome found in more than half of people with PD analysed. Data from eleven clinical trials, involving a total of 973 people with PD, were analysed. There were differences according to the diagnostic test performed and geographical distribution, with the subgroup in Western countries having a higher proportion of SIBO compared to those in Eastern countries, a difference most likely explained by immunological and metabolic peculiarities, but especially by dietary habits. The diagnosis of SIBO was more frequent in studies using lactulose for the breath test (51%) compared to those using glucose (35%) [172]. The identified causes of SIBO were structural and intestinal motility changes, use of pharmacological products (especially antibiotics) that alter the integrity of the intestinal mucosa. Alteration of permeability due to the inflammatory reaction triggered, leads to overexpression of AS, which in turn promotes blood-brain barrier alteration, neuroinflammation, and apoptosis of neurons in the substantia nigra. Its misfolding further alters the integrity of the intestinal mucosal barrier, a self-sustaining vicious circle. Altered gastric motility, with the development of gastroparesis leading to delayed elimination of food and bacteria, is a predisposing factor for SIBO. Recurrent or long-term use of proton pump or histamine inhibitors, metabolic diseases (e.g. diabetes mellitus through damage to the enteric nervous system causes gastroparesis and small bowel dysmotility) and inflammatory bowel diseases, as well as structural abnormalities acquired through surgery or complications thereof, are predisposing factors for SIBO. Clinical signs are diverse, non-specific, and changes in appetite, early satiety, bloating, abdominal pain, diarrhoea or constipation are often reported. Persistent SIBO leads to complications due to long-lasting poor digestion, malabsorption due to decreased capacity to assimilate intestinal villi or due to inflammation of the intestinal mucosa. All these produce mineral deficiencies (especially iron) or hypovitaminosis (vitamin B12, A, D, E); the most common is vitamin B12 (cobalamin) deficiency, which is absorbed in the ileum after binding to the specific protein. The presence of SIBO causes competitive metabolism of cobalamin by anaerobic bacteria, but also deficient absorption of the specific protein, thus decreasing the total amount of vitamin B12. At the opposite pole is hypervitaminosis, due to excessive synthesis of folate by bacteria in the small intestine. These complications lead to fatigue, weight loss, retinopathy, neuropathy and

steatosis. Although rare, alteration of coagulation parameters and impairment of T-cell immune function may occur.

The PhD thesis comprises 2 studies, through which I aimed to evaluate patients with PD in order to clarify the association between gut microbiota-related factors and certain clinical and biological features, degree of disability, disease severity, and the correlation of peripheral haematological markers of inflammation with severity of parkinsonism and other features of sporadic Parkinson's disease. The data provided by this PhD thesis will also have potential therapeutic importance for symptomatic purposes, as the gut microbiota can be manipulated to improve motor symptoms and response to symptomatic treatment. Studies show that the first symptoms of PD appear as early as 12-14 years before affected individuals meet the clinical diagnostic criteria used in common practice (which allow diagnosis of the disease only in the presence of motor manifestations). These early manifestations are non-motor, through olfactory and gastrointestinal tract dysfunction. In the prodromal phase, hyposmia, constipation, apathy, depression are frequently reported. In evolution, non-motor symptoms worsen, and motor symptoms appear, usually unilaterally. Of particular interest is the accumulation of diagnostic data for the detection of PD in the prodromal phase; diagnosis at this stage would reduce neuronal loss, thus leading to a markedly improved clinical status, favouring the effectiveness of disease-modifying treatments.

The performance of this research had the hypothesis that, according to a recent study, up to 67% of people with PD develop SIBO. The presence of SIBO, with both methane-producing and hydrogen-producing bacteria, is associated with the severity of Parkinson's syndrome but not with the severity of complications. There is evidence that the microbiota of people with PD produce less hydrogen, which has a hypothesized negative impact on neurodegeneration progression given the possible neuroprotective effect of hydrogen related to neutralization of hydroxyl radicals and decreased inflammatory stress and decreased expression of proinflammatory factors. This makes it plausible to hypothesize that people with advanced PD who have hydrogen-producing SIBO have less inflammatory changes in the gut and thus less changes in gut barrier integrity compared to people with advanced PD who do not have hydrogen-producing SIBO. More than 80% of people with PD have slowed intestinal transit and chronic constipation (i.e. predisposing factor for SIBO), which in most cases precedes the onset of motor manifestations. The occurrence of SIBO, with both methane-producing and hydrogen-producing bacteria, is associated with the severity of

Parkinson's syndrome. In PD, SIBO is related to non-motor symptoms and motor complications due to changes in the gastrointestinal mucosa through the development of inflammation.

Hydrogen (H2) and methane (CH4) are not produced by human cells but exclusively by bacteria, they easily cross membranes and are rapidly absorbed in the intestine where they enter the blood and exhaled air. Thus, breath tests that measure the amount of hydrogen and methane in exhaled air after carbohydrate (used by bacteria) intake are also used to diagnose SIBO. Detection of SIBO and initiation of antibiotic therapy (rifaximin), seems to ameliorate motor fluctuations. H2 is one of the main endogenous gases, produced by intestinal bacteria as a result of food fermentation (Blautia sp Clostridium spp) [163]. Hydrogen sulphide (H_2S)-producing bacterial species are numerous in the colonic microbiome of people with PD. H_2S has the ability to penetrate intracellularly, where, in excessive amounts, it can release mitochondrial cytochrome C protein, and increase levels of cytosolic iron and oxygen-reactive species. These mechanisms promote the formation of misfolded AS, with accumulation of fibrils intracellularly. Additionally, H_2S can affect erythrocyte and lymphocyte levels (with a role in peripheral inflammation), as well as urate metabolism, a potent endogenous antioxidant agent. In 2019, a study published by Hertel et al. examined the gut microbiome of healthy individuals compared to those with PD, finding higher levels of H_2S in the latter, driven by the bacteria Bilophila wadsworthia and Akkermansia muciniphila [143, 164]. An increased level of H_2S was also reported by Greco and co-workers in 2021 in the cerebrospinal fluid of people with PD. Methane-producing bacterial species account for approximately 15% of the microbial population. In recent decades, several methane-producing species have been detected in numerous tissue types (at intestinal, colonic, faecal or brain abscess level). They are quantitatively minor species in the gut microbiome, interacting symbiotically with other bacteria. They have local and remote modulatory effects on the immune system and a protective role against pathogenic microorganisms in the digestive system. Although their function in pathological mechanisms is not fully understood, methane-producing bacteria are now considered to play a role in a wide range of diseases, from those with inflammatory substrates (irritable bowel syndrome) to metabolic or neoplastic diseases [166, 167].

As part of study 1, I assessed small intestinal bacterial overgrowth syndrome in people with sporadic Parkinson's disease. In PD, SIBO is linked to non-motor symptoms and motor complications due to changes in gastrointestinal mucosa through the development of inflammation. The gut microbiome, which contains over 100 trillion microorganisms distributed

in a particular and individual pattern, plays an essential role in the unfolding of physiological mechanisms and the development of pathological ones. The communication between the gut microbiota and the brain is based on Braak's hypothesis, where a pathogen is involved in the aetiopathogenesis of PD that penetrates the nasal mucosa, reaches the gut, where it causes conformational changes in the AS and is then transmitted upwards through the vagus nerve pathway to the brain. This theory was supported by anatomopathological findings that identified the presence of Lewy bodies in the enteric nervous system and altered AS in the Auerbach and Meissner plexuses. Deposits of phosphorylated AS were identified in the ganglia, nerve fibres in the submucosal layer, gastric, duodenal and colonic enteric fibres in individuals with prodromal or motor clinical signs typical of PD. In order to conduct the study, I used the human and logistic resources available at the Colentina Clinical Hospital in Bucharest.

The test regarded as the gold standard for the diagnosis of SIBO is the presence of $\geq 10^3$ CFU in fluid sampled from the small bowel. For the diagnosis of SIBO I used the respiratory tests for H2 and CH4 levels, a method based on oral administration of glucose (75 g), with subsequent measurement over 2 hours of hydrogen in exhaled air (channelled over the reading sensor using a dedicated pipe). The tests were performed with the Gastrolizer® and GastrCH4H2ECK® devices. The rise of methane above 10 ppm and hydrogen above 20 ppm in exhaled air 1.5 hours after 75 grams of orally administered glucose was considered the diagnostic limit for H-SIBO and CH4-SIBO. The 20 ppm cut off has a specificity of 90% and sensitivity of 81% compared to bacterial counts in intestinal fluid (i.e., the reduced sensitivity derives from the fact that some bacteria that may overpopulate the small intestine produce exclusively methane).

As part of the presented research, I assessed the correlations between the presence of SIBO with hydrogen-producing bacteria (H-SIBO) and methane (CH4-SIBO) in patients with advanced PD participating in the AIM-BP study - demographics, disease characteristics, therapy followed, association with peripheral inflammation markers and gastrointestinal disorders recorded. The study included 31 people with PD and 31 people in the control group. Individuals with a diagnosis of advanced PD - defined as Hoehn and Yahr stage >/= 2 and/or the presence of motor complications of dopaminergic replacement therapy (i.e., motor fluctuations and dyskinesias), or the onset of motor manifestations of PD and/or diagnosis at age > 50 years, and no exclusion criteria. The latter were the age <50 years at the time of symptom onset or diagnostic classification, antibiotic administered in the last 3 months (anamnestically), probiotics/prebiotics and/or enema

and/or intestinal paralysers, etc., administered consistently in the past month (anamnestically), consistent bowel symptomatology other than related to slowed intestinal transit (anamnestically); bowel or systemic infections in the past 6 months (documented); infectious diseases including COVID-19; consistent contact in the past month (i.e., cohabitant, daily interaction, etc.) with person with active C. difficile infection/enterocolitis (anamnestically); chronic/concurrent systemic, gastrointestinal, or neurologic immune-mediated diseases (documented); concurrent cancer diagnosis (documented); immunosuppressive or immunomodulatory treatment (documented); any disability that significantly interferes with clinical assessment and/or decision making ability to provide assent/consent to study participation (i.e., language disorder, major neurocognitive disorder etc - documented or as assessed by the evaluating researcher); refusal to participate in this study; other known or suspected neurodegenerative disease at the time of enrolment. The control group included individuals aged >/= 50 years, without a diagnosis or suspicion of PD, and who did not meet any of the exclusion criteria listed above.

Demographic and clinical characteristics, presence of SIBO, presence of gastrointestinal disorders and their type were analysed in both groups. For 23 people with PD I used the Gastrolyzer® (detection of hydrogen levels in exhaled air) and for 11 I used the GastrCH4H2ECK® **(**detection of hydrogen and methane levels in exhaled air**)**; 3 of the patients were tested with both devices.

In the group of people with PD, the age group 61-70 years was predominant, followed by the age group 71-80 years; people over 80 years were in the smallest proportion in the analysed group. The gender distribution in the analysed group had 52% male and 48% female distribution. I found that a longer period since disease onset is highly statistically significantly correlated with a higher Hoehn and Yahr stage (rho=0.542, p=.001) and with the occurrence of complications (p=0.698, p<.0001), and a highly statistically significant correlation between the presence of complications and disease stage (rho=0.544, p=.001). As for the oxidative stress hypothesis, a statistically significant correlation was observed between higher uric acid value and males (rho=0.440, p=.01), inversely proportional to disease duration (rho=0.560, p=. 001), meaning that patients with higher uric acid values are patients with shorter disease duration; a statistically significant correlation between uric acid value and Hoehn&Yahr stage (rho=0.508, p=. 003), meaning that patients with higher uric acid values are classified in a lower H&Y stage; a statistically significant correlation

between uric acid value and the presence of tremor (rho=0.397, p=.02), meaning that patients with higher uric acid values do not experience tremor or stiffness as a dominant phenotype.

SIBO was found in 52% of people with PD as an overall analysis of the whole group. A statistically significant correlation was observed between the presence of SIBO and early satiety (rho=0.391, p=.02), bloating (rho=0.361, p=.04) and constipation (rho=0.436, p=.01). As for the distribution according to the gastrointestinal disorders present in the group of people with PD, the presence of constipation and abdominal pain, followed by bloating, was observed in equal proportions. Decreased appetite was the least reported, and the presence of accelerated diarrhoeal transit was not reported by any patient. On statistical analysis of SIBO≥ 20 ppm, a statistically significant correlation (r=0.497, p=<.0001) was observed between patients in the control group and the presence of SIBO≥ 20 ppm. As for the mean value of H2 measured at 1h30 in the two groups, a statistically significant difference is observed, meaning that statistically significantly higher values (p<.0001) were measured in the study group than in the control group. Note that the mean value of NLR in the two groups is statistically significantly different, meaning that statistically significantly higher values (p<.0001) were measured in the study group than in the control group, with similar data being obtained for PLR (p=.0002); the mean value of MLR in the two groups is statistically insignificantly different, meaning that statistically insignificantly higher values (p=.09) were measured in the study group than in the control group. The distribution according to the number of patients with increased NLR, PLR, MLR values is observed, compared between the two groups, with these ratios having higher values in people with PD. There are statistically significant differences between the 2 groups in terms of mean age, in the control group there are significantly younger patients, significantly fewer neurocognitive disorders, mean values of NLR, PLR and MLR are significantly lower in the control group. Gastrointestinal disorders are present only in significantly fewer subjects in the control group as compared to the study group. Also, SIBO is present in significantly more patients than in the control group.

The second study focused on the correlation of peripheral haematological markers of inflammation with the severity of parkinsonism and other features of sporadic Parkinson's disease. I conducted a cross-sectional descriptive observational study on electronically available data collected during admissions to the Neurology Departments of Colentina Clinical Hospital in the period 2018-2021 to investigate the correlation between haematological indices NLR, MLR and PLR, considered peripheral inflammation markers, and idiopathic/sporadic PD characteristics. The

hypothesis underlying this study was that, although multifactorial, inflammatory mechanism seems to be involved in pathogenesis and disease progression [33, 50]. Recent studies have demonstrated correlations between NLR and motor staging in sporadic/idiopathic PD [120,180, 181,182]. NLR, MLR and PLR are indicators established on the basis of haemogram, an analysis that is routinely performed, inexpensive and readily accessible, and thus easy to obtain in routine clinical practice. They are considered markers of peripheral inflammation in multiple diseases, from vascular, osteoarticular and metabolic pathology, with a role in neurodegenerative diseases, a role that has been reconsidered relatively recently. In addition to their potential biomarker value, which could contribute to increasing the sensitivity and specificity of current diagnostic criteria for neurodegenerative diseases, the association of these markers with certain pathologies offers the opportunity to investigate potential new therapeutic interventions for symptomatic or evolutionary improvement [120].

In this study, correlations of haematological markers of inflammation with duration and characteristics of PD (markers of peripheral inflammation involved in assessing the degree of disease activity, progression, prognosis) were assessed. Based on the inclusion and exclusion criteria detailed above, I included in the analysis 107 patients (of whom 64.5% males), with a mean age of 70 years. I found correlations between NLR and age ($r_s = 0.377$, $p < 0.001$), between NLR and cerebrovascular disease ($r_s = 0.322$, $p < 0.001$), between MLR and PLR and Hoehn and Yahr stage ($r_s = 0.259$, $p = 0.018$, respectively $r_s = 0.257$, $p = 0.019$) and between PLR and motor complications ($r_s = 0.303$, $p = 0.003$).

Conclusively, data obtained in individuals with PD revealed the presence of a chronic inflammatory status and a gut microbiome disorder, translated by the identification of SIBO and gastrointestinal disorders. These correlate with a more advanced degree of disease, the presence of motor and non-motor complications, and the presence of neurocognitive disorder. The data provided by this PhD thesis are of importance for symptomatic approaches, as modulation of the gut microbiome is currently a therapeutic trend with the potential to increase quality of life by improving motor symptoms and response to symptomatic treatment.

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List of published papers

1. **Small intestinal bacterial overgrowth as potential therapeutic target in Parkinson's disease.**

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International Journal of Molecular Sciences.

Int. J. Mol. Sci. 2021, 22, x. https://www.mdpi.com/1422-0067/22/21/11663

2. **Serum Uric Acid Levels in Parkinson's Disease: A Cross-Sectional Electronic Medical Record Database Study from a Tertiary Referral Center in Romania.**

Adela Dănău , Laura Dumitrescu , Antonia Lefter and Bogdan Ovidiu Popescu

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