UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
„CAROL DAVILA“ DIN BUCUREȘTI

Str. Dionisie Lupu 37, sector 2, București, 020021, România, www.umfcd.ro, email: rectorat@umfcd.ro

“CAROL DAVILA” UNIVERSITY
OF MEDICINE AND PHARMACY, BUCHAREST
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THE IMPACT OF NEURODEGENERATION ON BLOOD PRESSURE IN PATIENTS WITH PARKINSON'S DISEASE

SUMMARY OF THE PHD THESIS

PhD Supervisor:
PROF. BOGDAN OVIDIU POPESCU

PhD Student:
DELIA TULBĂ

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The Impact of Neurodegeneration on Blood Pressure in Patients with Parkinson's Disease

Summary

My PhD thesis encompasses two parts: I. a narrative literature review aiming to synthesize the current state of knowledge on blood pressure (BP) regulation in Parkinson's disease (PD), especially when cardiovascular autonomic dysfunction (CAD) and high blood pressure (HBP) are superimposed (the brain-heart axis), and about the influence of intestinal dysbiosis and inflammmation/permeability on PD +/- CAD and HBP (the gut-brain-heart axis); II. personal contributions, in which we conducted two systematic reviews, two descriptive (cross-sectional) studies and one analytical (case-control) study, aiming to explore the triangular relationship between PD, CAD and HBP, and their mutual interplay with the intestinal milieu, further shaping the concept of gut-brain-heart axis.

I. Literature Review

1. Parkinson's Disease and Blood Pressure (The Brain-Heart Axis)

Parkinson's Disease

In this chapter, I compiled the latest evidence on PD etiopathogenesis, emphasizing the progress and the challenges in our understanding of this complex disease. With the new biological definitions and staging systems of PD gaining considerable interest [1, 2], hopes for precision (disease-modifying) treatments targeting biologically defined populations have raised [3], despite several caveats highlighted by Jankovic et al. [4].

Cardiovascular Autonomic Dysfunction in Parkinson's Disease

In this chapter I covered the importance of non-motor manifestations in PD. Out of these, CAD is of particular importance considering that dysregulation/degeneration of the peripheral autonomic nervous system (ANS) begins early in the disease (at least in the body-first (bottom-up) phenotype), and early pathology in the ANS could be a route by which α-synuclein (αSyn) aggregation is spread both to and from central nervous system (CNS) [5]. Moreover, CAD has diagnostic value; it has been proposed as a clinical biomarker for the body-first subtype of PD [6], and could assist the early differential diagnosis in synucleinopathic and tauopathic parkinsonisms and their subtypes [7-9].

Cardiovascular dysautonomia is responsible for global circulatory alterations with abnormal BP control, such as orthostatic hypotension (OH), supine hypertension (SH), postprandial hypotension (PH), altered circadian BP rhythm (nocturnal hypertension (NH) and non-dipping pattern), and abnormal BP variability [10]. In PD, CAD displays a broad variety of manifestations that range from the asymptomatic non-dipping BP pattern to frequent falls with serious traumatic injuries or sudden cardiac death, and early-onset CAD is associated with a more rapid disease progression and shorter survival [11].

Parkinson's Disease and Hypertension Interactions

The deleterious effects of CAD are additionally endorsed by HBP, which is likely to occur in PD patients, especially in aging populations. Coexistent HBP alters BP control even further: antihypertensive treatment worsens OH [12], which is responsible for falls (with subsequent head trauma and bone fractures), cognitive decline, cardiovascular events and physical deconditioning [13], whereas pressor agents used in OH aggravate HBP, SH and NH, possibly eliciting end-organ damage [14, 15]. The interplay between PD +/- CAD and HBP is also emphasized by mutual influences on disease risk and/or progression, the effects of antiparkinsonian drugs on BP profiles and those of antihypertensive treatment on PD emergence/progression, which add new dimensions to the brain-heart axis.

2. The Influence of Intestinal Inflammation/Permeability and Dysbiosis on Parkinson's Disease and Hypertension (The Gut-Brain-Heart Axis)

Intestinal Inflammation/Permeability in Parkinson's Disease

Following the identification of αSyn inclusions in the neurons of Auerbach's and Meissner's plexuses [16, 17] early in the course of PD [18], the caudo-rostral transmission of αSyn from the gut to the CNS through vagal connections has been hypothesized and subsequently demonstrated [19-21]. Hawkes et al. proposed the dual-hit hypothesis, in which a neurotropic pathogen, possibly viral, capable of inducing αSyn misfolding and aggregation, enters the brain via two routes: nasal and gastrointestinal (where it penetrates the epithelial lining and reaches the submucosal and myenteric plexuses) [22].

Scarce data from in vitro and in vivo experiments as well as clinical studies support the hypothesis of intestinal inflammation and dysregulation of the intestinal barrier structure with subsequent intestinal permeability in PD [23, 24]. Theoretically, this could facilitate the entry of antigens and other macromolecules into the lamina propria, resulting in immune system activation and initiation/perpetuation of inflammatory responses, namely "gut leakiness" [25]. Moreover, the subsequent exposure of the enteric nervous system (ENS) to oxidative stress could create a breach that might favour αSyn aggregation [26].

Intestinal Inflammation/Permeability in Hypertension

Intestinal microbial dysbiosis with deleterious functional and metabolomic changes also occur in patients with HBP, including intestinal inflammation and increased barrier permeability [27].

Intestinal Inflammation/Permeability Biomarkers

In clinical practice, various serum/fecal biomarkers of intestinal inflammation and intestinal permeability/bacterial translocation have been employed. In this regard, I reviewed the

characteristics and importance of serum and fecal calprotectin (S-Cal and F-Cal), zonulin (S-Zon and F-Zon) and lipopolysaccharide-binding protein (S-LBP).

Intestinal Dysbiosis in Parkinson's Disease

Increasing evidence points toward a role of dysregulated microbiota in PD pathogenesis, which is thought to elicit local and systemic inflammation by translocation of bacteria and production of proinflammatory metabolites [26]. Numerous changes in the bacterial taxa have been reported in PD patients [28, 29].

Small intestinal bacterial overgrowth (SIBO) is a particular form of small intestine dysbiosis encompassing abnormal and excessive numbers of bacteria in the small bowel, usually associated with gastrointestinal symptoms such as abdominal discomfort, diarrhea, bloating and weight loss due to malabsorption [30, 31]. In has been hypothesized that SIBO might play a role in the pathophysiology of levodopa-induced motor fluctuations [32].

Intestinal Dysbiosis in Hypertension

Significant compositional changes (diversity and richness) of gut microbiota have been described in HBP patients [27]. Altered gut microbiota has been linked to cardiovascular disorders (including HBP) occurrence and progression via various dysregulated pathways [33].

Intestinal Dysbiosis Biomarkers

Gut microbiota is mainly explored through next generation sequencing techniques such as whole-genome shotgun sequencing and 16S ribosomal ribonucleic acid (rRNA) sequencing [34]. A combination of culture and 16S rRNA sequencing, named culture enriched molecular profiling, cand also be employed in capturing the diversity of gut microbiota [35].

Small intestinal bacterial overgrowth is currently diagnosed by two methods: direct testing via quantitative cultures of duodenal or jejunal aspirates and/or indirect assessment via a carbohydrate (using different carbohydrate substrates, such as lactulose and glucose) breath testing [36, 37].

II. Personal Contributions

3. Hypotheses and General Objectives

Considering the triangular relationship between PD, CAD and HBP, subsumed to the brain-heart axis, with possible interactions within and across various neural, mechanical and biochemical pathways [38], we hypothesized that patients with PD have abnormal BP patterns/profiles mainly due to CAD and/or superimposed HBP. Moreover, we assumed that altered gut microbiota and intestinal inflammation/permeability might be the missing link in this setting, shaping the concept of gut-brain-heart axis.

We aimed to thoroughly investigate the relationship between PD, CAD and HBP, focusing on their interactions at various levels. Moreover, we planned to take a closer look at the intestinal inflammation/permeability biomarkers and SIBO in patients with PD (+/-CAD) and HBP, and to determine their significance in regard to disease severity.

4. General Methodology

We conducted two systematic reviews, two descriptive (cross-sectional) studies and one analytical (case-control) study. The project embedding all original studies was approved by the Local Ethics Committee (Moni**to**ring of Cardiovascular **P**arameters in Patients with **Park**inson's Disease and Arterial Hypertension, TOP PARK, No. 7/02.03.2023). In the original research, the studied population consisted of patients with sporadic PD and primary HBP, without diabetes mellitus or other causes of secondary CAD.

Patient assessment included a comprehensive medical history review and neurological examination, clinical scales for motor and non-motor status and profiles, and disability rating scales. Each patient was subjected to a standard orthostatic BP test and underwent blood tests and urinalysis, carotid/vertebral ultrasound and transcranial Doppler, electrodiagnostic testing

including nerve conduction studies +/− needle electromyography, standard electrocardiogram (ECG), 24-h ECG Holter, and 24-h ambulatory blood pressure monitoring (ABPM); whenever possible, a hydrogen (H_2)/methane (CH_4) breath testing was performed. Additionally, the last 20 patients included also delivered a stool sample.

Database design and data analysis were performed using IBM SPSS Statistics 26. Considering the non-normal distribution of data, nonparametric tests were used. Hypothesis testing was two-tailed and statistical significance was defined as $p < 0.05$.

5. Blood Pressure Patterns in Patients with Parkinson's Disease: a Systematic Review

Hypothesis and Objectives

In this systematic review, we aimed to describe BP patterns reported in patients with PD, as measured by 24-h ABPM, in conjunction with HBP and CAD manifestations. We hypothesized that these patients have abnormal BP patterns mainly due to CAD and/or superimposed HBP.

Materials and Methods

We designed a systematic review based on the following research question: *"What are the BP patterns identified by 24-h ABPM in patients with PD?"*

The target population consisted of adult patients diagnosed with PD. The intervention was ABPM performed during a minimum of 24 hours. The outcomes were BP profiles (HBP, OH, SH, NH, dipping status) and BP measurements (mean BP during daytime/nighttime/24-h, median variation coefficient and BP load).

We conducted a systematic search on the PubMed database with the following search strategy:

((((((((((("blood pressure"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields])) OR "blood pressure"[All Fields]) OR "blood pressure determination"[MeSH Terms]) OR (("blood"[All Fields] AND "pressure"[All Fields]) AND "determination"[All Fields])) OR

"blood pressure determination"[All Fields]) OR ("blood"[All Fields] AND "pressure"[All Fields])) OR "blood pressure"[All Fields]) OR "arterial pressure"[MeSH Terms]) OR ("arterial"[All Fields] AND "pressure"[All Fields])) OR "arterial pressure"[All Fields]) OR ("blood"[All Fields] AND "pressure"[All Fields])) AND ((((((((((("monitors"[All Fields] OR "monitorable"[All Fields]) OR "monitored"[All Fields]) OR "monitoring"[All Fields]) OR "monitorings"[All Fields]) OR "monitoring, physiologic"[MeSH Terms]) OR ("monitoring"[All Fields] AND "physiologic"[All Fields])) OR "physiologic monitoring"[All Fields]) OR "monitor"[All Fields]) OR "monitorings"[All Fields]) OR "monitorization"[All Fields]) OR "monitorize"[All Fields]) OR "monitorized"[All Fields]) OR "monitors"[All Fields])) AND ("Parkinson's disease"[All Fields] OR "Parkinson Disease"[MeSH Terms]).

Results

Forty studies fulfilled the inclusion criteria, all with a cross-sectional design. A total number of 3090 PD subjects were enrolled, with a sex ratio of 1.08. The mean age of patients was > 60 years in all the studies, with a mean duration of PD (i.e., from the onset of motor symptoms) ranging from 1 to 18.4 years; mean value of MDS-Unified Parkinson's Disease Scale (MDS-UPDRS) Part III spanned from 14.5 to 36.2, and Hoehn and Yahr (H & Y) stage from 1.5 to 3.6. Various studies enrolled control groups (healthy control subjects and/or patients with HBP, pure autonomic failure, Lewy body dementia, multiple system atrophy, progressive supranuclear palsy, drug-induced parkinsonism, scans without evidence of dopaminergic deficit or mild cognitive decline (SWEDDs)) or performed an analysis of PD subgroups (i.e., with and without autonomic failure, according to dipper and non-dipper profile, with or without depression, according to the duration of the disease).

We recorded the intake of vasoactive drugs, with considerable differences in reporting them. Some studies specifically withheld them during ABPM, with possible implications for BP profiles and measurements. Notably, dopaminergic therapy did not seem to increase the occurrence/prevalence of OH, SH, NH and non-dipping status [39].

Blood pressure profiles were frequently altered in these patients: 938 patients (38.13% of the number of patients who were evaluated for this issue) had HBP, 941 patients (38.67%) had OH, whereas 445 patients (27.76%) had SH. The circadian blood rhythm was also

dysregulated, reverse dipping, reduced dipping and extreme dipping being described in 477 (40.45% of the patients evaluated for this), 310 (35.67%) and 23 (5.09%) subjects, respectively.

Significant correlations were found between BP profiles and patterns and various indicators of disease severity. Orthostatic hypotension was associated with higher rates of depression [40, 41] and fatigue [42], as well as more severe cognitive impairment [40, 42-45], autonomic [44] and motor symptoms [43]. Supine hypertension occurrence was significantly associated with carotid artery thickening [46]/arterial stiffness [47] and an increased number of cerebral microbleeds in any brain region [48]. Nocturnal hypertension was an independent predictor of arterial stiffness [47]/carotid artery thickening [46] and larger extent of white matter lesions in early PD [49]. Parkinson's disease patients with reduced dipping were more prone to psychotic symptoms [50], whilst those with reverse dipping had more severe non-motor manifestations such as cognitive decline [40, 42, 51, 52], anxiety [40, 51] and autonomic symptoms [40, 51, 53]. Moreover, this profile was strongly associated with CAD, after adjusting for age, sex, disease duration, HBP and intake of antihypertensives, with a higher sensitivity and accuracy than OH [54].

Conclusion

Cardiovascular autonomic dysfunction and HBP are common findings in patients with PD and have a negative impact on their quality of life, functionality and life expectancy, underpinning the need for proper assessment and management. The ABPM is an accessible and feasible method for evaluating BP patterns. In PD patients, it is able to capture the extent of cardiovascular homeostasis disruption throughout a day by offering insights into BP fluctuations and BP profiles with regard to patient's routine activities.

6. Shared Molecular Targets in Parkinson's Disease and Hypertension: a Systematic Review

Hypothesis and Objectives

We aimed to assess the role of antihypertensive drugs in PD pathogenesis (both emergence and progression). We hypothesized that they might exert neuroprotective and/or disease-modifying effects in a dose and time-dependent manner.

Materials and Methods

We designed a systematic review centered on the following research question: *"Does HBP medication pertaining to major antihypertensive drug classes exert neuroprotective and/or disease-modifying effects in a dose and time-dependent manner in adult patients with sporadic PD regardless of BP values?"*

The defined target population (P) consisted of adult patients diagnosed with sporadic PD. The intervention (I) was intake of drugs pertaining to one of the major antihypertensive drug classes (i.e., β-blockers (BBs), diuretics, calcium-channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs)), in any regimen. The comparator (C) involved subjects not receiving the intervention. The outcome (O) was either the occurrence (in patients receiving antihypertensive drugs before the motor onset and diagnosis of PD) or the progression of PD (in patients receiving antihypertensive drugs afterwards).

We performed a systematic search on the PubMed database using the following search strategy: *("Vasodilator Agents" [MeSH Terms] OR ("Angiotensin-Converting Enzyme Inhibitors" [MeSH Terms] OR "Angiotensin II Type 1 Receptor Blockers" [MeSH Terms] OR "Angiotensin Receptor Antagonists" [MeSH Terms] OR "Calcium Channel Blockers" [MeSH Terms] OR "Dihydropyridines" [MeSH Terms] OR "Diuretics" [MeSH Terms] OR "Adrenergic beta-Antagonists" [MeSH Terms] OR "Sympatholytics" [MeSH Terms])) AND ("parkinson*" [Title/Abstract] OR "Parkinson Disease" [MeSH Terms] OR "Parkinsonian Disorders"[MeSH Terms])*.

We divided the outcome into two categories, depending on the timeframe of antihypertensive drug intake relative to PD onset (before or afterwards) - neuroprotective (i.e., the antihypertensive drug is a protective factor for PD occurrence) or disease-modifying (i.e., the antihypertensive drug has a beneficial effect on the course of PD) effect. Two confounders were carefully assessed: drug-induced parkinsonism and symptomatic effect.

Results

Twenty studies fulfilled the inclusion criteria, all of them being analytical, both observational (case-control and cohort studies, either retrospective or prospective) and interventional (randomized controlled trials).

Fifteen studies investigated whether the exposure to antihypertensive agents is a protective factor for PD emergence (neuroprotective effect), whilst five studies explored the effect of antihypertensive therapy on PD progression (disease-modifying effect).

Beta-blockers. There are conflicting results regarding the role of BBs in the emergence of PD. Two studies reported an increased risk of PD among BBs users [55, 56], four other studies found an association between short-term use of BBs and PD emergence, indicating a reverse causation or protopathic bias (i.e., association likely driven by the use of BBs for symptoms of early and yet undiagnosed PD such as tremor) rather than a real causative link between BBs use and PD occurrence [57, 58], and three studies addressing the same issue indicate no association between BBs use and PD emergence [59, 60]. Only one study inquired the role of BBs as disease-modifying treatment and suggested no association in this regard [61].

Diuretics. The only study that addressed the effect of diuretics use in PD emergence found a positive association that was not time-dependent [59]. We found no studies addressing the role of thiazide and thiazide-like diuretics in PD progression.

Angiotensin-converting enzyme inhibitors. All in all, the studies inquiring whether ACEIs use is related to PD emergence suggest that there is no association in this regard. Both studies addressing ACEIs as potential disease-modifying treatment in PD seem to imply that ACEIs slow the progression of PD, but this conclusion is questionable since one of the studies has a cross-sectional design (which does not allow to establish a causal relationship between the use of ACEIs and fewer falls in PD) [61] and the other one only included six patients [62].

Angiotensin II receptor blockers. The conclusion of the studies that explored the effect of ARBs intake on PD emergence is that ARBs do not seem to have a neuroprotective effect in PD, but a dose-dependent effect might be involved according to Lee et al. [63]. The highest cumulative doses of ARBs were associated with a lower risk of PD, even after stratifying the

population according to age and gender [63]. Although there is no report of ARBs influencing the progression of PD, it is an issue worth studying.

Calcium-channel blockers. The results of the studies that investigated the effect of exposure to CCBs on PD occurrence are equivocal. Five studies concluded that these drugs reduce the risk of incident PD, whereas four studies deny any effect on PD emergence. Moreover, the authors of one study pertaining to the former category admit that the results could reflect a symptomatic effect (by preventing the development of clinical symptoms of early disease) rather than a neuroprotective one, since they notice a rapid disappearance of effects upon discontinuation of CCBs [64]. Two studies imply that CCBs intake does not alter the progression of PD.

Conclusion

Although the studies addressing the potential neuroprotective and/or disease-modifying effect of antihypertensive drugs in PD reported conflicting results mainly because of heterogeneous protocols and population, there is proof that they might offer potential therapeutic solutions, but this hypothesis needs further studying and testing. Moreover, perhaps it would be wise to evaluate the effect of combination antihypertensive therapies in PD emergence and/or progression.

7. Cardiovascular Dysautonomia in Patients with Parkinson's Disease and Hypertension: a Cross-Sectional Study

Hypothesis and Objectives

Considering that PD and HBP are often comorbid and patients with PD frequently develop CAD, we aimed to explore this triangular relationship. We hypothesized that in patients with sporadic PD and primary HBP, without diabetes mellitus or other secondary causes of autonomic failure, CAD (related to PD) is associated with significant disability (primary outcome).

Moreover, we sought associations between CAD and PD characteristics (including non-motor phenotypes), as well as cardiovascular comorbidities (secondary outcome).

Material and Methods

We conducted a unicentric cross-sectional study enrolling patients with PD and HBP, without diabetes mellitus or other secondary causes of CAD.

In the multivariate analysis (logistic regression), we adjusted for the variables that were associated with disability in the univariate analysis (i.e., neurogenic OH, H & Y stage, levodopa equivalent daily dose (LEDD), Montreal Cognitive Assessment (MoCA score), and PD duration). They were selected as covariates by the "enter" method, with disability measured on the Modified Rankin Scale (mRS) (good outcome, no assistance: mRS grade 0–2; and bad outcome, assistance needed: mRS grade 3–6) as a dependent variable.

Results

We included 47 patients with sporadic PD and primary HBP, without diabetes mellitus or other causes of secondary autonomic failure. The mean age was 68.51 ± 7.86 years (48–83) and the majority were men (57.4%).

We recorded cardiovascular and cerebrovascular comorbidities, as well as detailed intake of cardioactive and vasoactive drugs. Apart from the antihypertensive drugs, we also recorded therapy with sympathomimetics, sympatholytics, parasympathomimetics, parasympatholytics, and psychiatric medications that could induce hemodynamic changes. Almost half of the patients (46.8%) had a history of grade 3 HBP. Beta-blockers and ACEIs were the vasoactive drugs most commonly prescribed (53.2% and 36.2%, respectively).

Data regarding PD course, severity, phenotype (both motor and non-motor), and therapy were also collected. The median duration of the disease was 9 years, ranging from recent motor onset to 30 years of motor disease course. The median MDS-UPDRS Part III score was 40. Motor fluctuations were almost as common as peak-dose dyskinesia (47.7% and 51.1%, respectively). A quarter of the patients complained of morning and/or night akinesia, whereas complex motor fluctuations were infrequent (unpredictable off in 9.3% of the cases and no on

in 11.4% of the cases). The median MoCA score was 24. Apart from cognitive decline, other non-motor symptoms were also very frequent: almost two-thirds of our patients reported constipation (67.4%), orthostatic dizziness (65.2%), urinary urgency (63%), and sleep onset and/or maintenance insomnia (61.7%). The majority of the patients were treated with oral levodopa (91.5%) and almost one-quarter (23.4%) used controlled-release formulations. Dopamine agonists were prescribed in almost 60% of the patients, type-B monoamine oxidase (MAO-B) inhibitors in 45%, and cathecol-O-methyltransferase (COMT) inhibitors in 35%. A quarter (N = 12; 25.5%) had a device-aided therapy.

One-third of the patients (34.9%) had axonal polyneuropathy detected with nerve conduction studies, out of which the majority had a primarily sensory involvement with distal and symmetric distribution.

The diurnal and nocturnal BP values were within the normal range in our group. However, the hyperbaric index was above normal reference for both systole and diastole during the daytime and only systole during the nighttime, which would suggest an inadequate control of HBP. The circadian rhythm of BP was also altered in our group, with 80.4% of the patients having a non-dipper profile (39.1% reduced dippers and 41.3% reverse dippers). The time-domain indices of heart rate variability (HRV) were within reference ranges.

Almost one-third of the patients (31.8%) were found to have neurogenic OH. Nevertheless, 65.2% of all the subjects reported orthostatic dizziness and 15.2% had a syncope history. In our group, 21.4% of the patients with OH were asymptomatic, whereas 56.6% of the patients with orthostatic symptoms did not have OH at repeated measurements. The two groups (with and without neurogenic OH) did not differ significantly in terms of demographic factors or general PD characteristics (including levodopa-induced motor complications and motor phenotype). All the patients with neurogenic OH were non-dippers, with significant differences from their counterparts with regard to nocturnal BP profiles ($p = 0.016$). Those with neurogenic OH reported constipation, pollakiuria, urinary urgency, and anxiety more often, whereas other individual non-motor features did not reach statistical significance between the two groups. However, the overall burden of non-motor symptoms quantified through Non-Motor Symptoms Scale (NMSS) and Non-Motor Symptoms Questionnaire (NMSQ) was conspicuous in those with neurogenic OH as compared to their counterparts ($p = 0.039$ and 0.020, respectively); so was the disability reflected by the mRS ($p = 0.010$). After adjusting for possible confounders,

neurogenic OH remained associated with disability (i.e., bad outcome or assistance needed: mRS > 2).

Patients with a non-dipper pattern of BP were significantly older than the dippers ($p = 0.016$). General PD characteristics, including motor phenotypes and levodopa-induced motor complications, did not differ between the two groups. However, some non-motor features, such as erectile dysfunction, loss of libido, and gustatory impairment, were more frequently encountered in non-dippers ($p = 0.034$, $p = 0.020$, $p = 0.040$, respectively). Univariate analysis did not find associations between age and these non-motor features; therefore, age is not expected to be a confounder. Moreover, the global non-motor burden rated on NMSS and NMSQ was also significantly higher in this group ($p = 0.005$ and 0.018, respectively). Cardiovascular comorbidities and polyneuropathy had similar distributions. Time-domain indices of HRV were slightly lower in dippers compared with non-dippers. This group also had significantly higher morning BP surge ($p = 0.001$).

Conclusion

Neurogenic OH could be considered a predictor of disability in PD patients with HBP, independently of disease severity (assessed by H & Y stage) and duration. To our knowledge, this is the first study to explore the relationship between primary HBP (assessed by 24-h ABPM) and neurogenic OH in PD patients without (other) secondary causes of autonomic dysfunction (including diabetes mellitus).

8. Biomarkers of Intestinal Inflammation and Permeability are Increased in Patients with Parkinson's Disease and Hypertension and Correlate with Clinical Manifestations and Disease Severity: a Case-Control Study

Hypothesis and Objectives

Considering the growing body of evidence on the role of intestinal inflammation and barrier dysfunction in the pathogenesis of PD (at least in the body-first subtype of disease) and HBP, we hypothesized that increased levels of serum and fecal biomarkers of intestinal inflammation (S-Cal and F-Cal) and permeability (S-Zon, F-Zon) and bacterial translocation (S-LBP) are associated with a more severe clinical course in patients with PD and HBP. Moreover, we assumed that these patients have higher levels of serum and fecal biomarkers of intestinal inflammation (S-Cal and F-Cal) and permeability (S-Zon, F-Zon) and bacterial translocation (S-LBP) compared with healthy controls.

Material and Methods

We conducted a unicentric case-control study enrolling patients with PD and HBP and sex-matched healthy controls. Exclusion criteria also comprised current/active gastrointestinal disorders, gastrointestinal surgery and intake of antibiotics, probiotics/prebiotics, antacids (including proton-pump inhibitors) and anti-inflammatory drugs (steroidal or non-steroidal, including analgesic-dose aspirin) within the last month. We also selected an individually sex-matched control group from a healthy control sample enrolled in a previous study, without prodromal symptoms/signs of PD or other neurological conditions [65].

Results

We subsequently enrolled 20 patients with sporadic PD and primary HBP, without diabetes mellitus and other causes of secondary CAD, with a median age of 71.5 years (56-78) and a sex ratio of 1:1.

The median duration of disease was 9 years, ranging from recent motor onset to 24 years of disease course. Most of the patients had already transitioned to H & Y stage 3 and the median MDS-UPDRS Part III score was 40.5 during OFF state. More than half were already experiencing levodopa-induced complications, out of which wearing off and peak-dose dyskinesia were the most frequent. Regarding non-motor features, urinary urge and nocturia were identified in 75% of the patients, anxiety, neurocognitive disorder, pollakiuria and rapid eye movement sleep behavior disorder (RBD) in 65% of the cases, and hyposmia in 50% of

them. The median LEDD was 870 mg and included oral levodopa in 90% of the patients, dopamine agonists in 50%, COMT inhibitors in 35%, and MAO-B inhibitors in 25%. One quarter of the patients were on device-aided therapies.

Carotid and/or vertebral atherosclerosis was the most frequent cardiovascular comorbidity in our sample (78.9%), followed by chronic kidney disease (65%) and dyslipidemia (60%). The median awake and asleep SBP and DBP values were within normal range, although 40% had been diagnosed with grade 3 HBP. Nevertheless, the majority were non-dippers (75%). More than one third of them had neurogenic OH (35%) and only 5% had concomitant SH. Beta-blockers were the most frequently prescribed cardioactive drugs (55%), followed by ACEIs (30%) and benzodiazepines (25%; only clonazepam was used in this group of patients).

Both median S-Cal and F-Cal levels as well as S-LBP were slightly increased in this group of patients, whereas median S-Zon and F-Zon levels were within normal range. Blood and fecal biomarkers of intestinal inflammation and permeability and bacterial translocation were significantly associated with various clinical manifestations and disease severity. After adjusting for possible confounders (i.e., factors associated with disability in the univariate analysis), S-LBP levels < 10 μg/mL (categorical variable) remained associated with disability (i.e., bad outcome or assistance needed: mRS > 2). Significant differences with reference to blood and fecal biomarkers of intestinal inflammation and permeability were identified between patients and controls (Figure 8.1.).

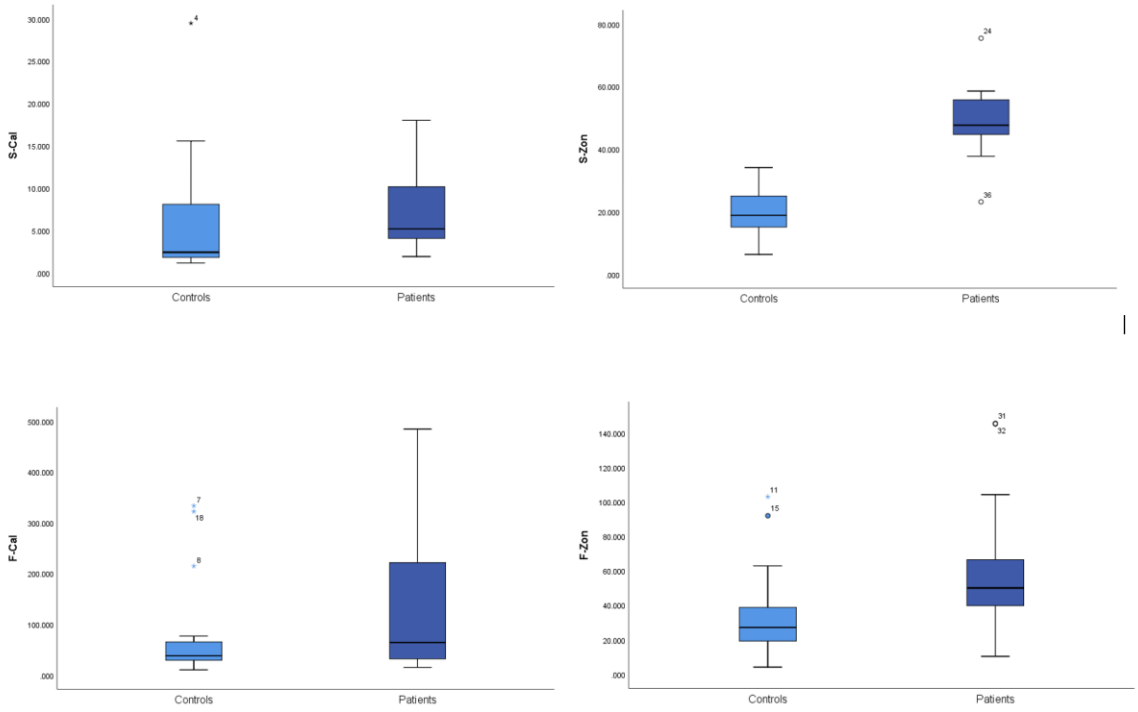

Figure 8.1. Distribution of intestinal inflammation and permeability biomarkers in patients versus control

Conclusion

Significantly higher levels of S-Cal, S-Zon and F-Zon were found in patients with PD and HBP compared with healthy controls. Moreover, reduced S-LBP levels could be considered a predictor of disability in PD patients with HBP, independently of disease severity and cognitive decline. However, the causal role of gut microbiota and intestinal inflammation on disease course in these patients is yet to be confirmed, and the interplay between PD and HBP in relation to intestinal inflammation warrants further study.

9. Association of Small Intestinal Bacterial Overgrowth with Disease Severity in Patients with Parkinson's Disease and Hypertension: a Cross-Sectional Study

Hypothesis and Objectives

Considering the growing body of evidence on the role of SIBO in the pathogenesis of PD and (maybe) HBP, we hypothesized that SIBO is associated with a more severe clinical course in patients with PD and HBP, in a gradient dependent manner.

Material and Methods

We conducted a unicentric cross-sectional study enrolling patients with PD and HBP, without diabetes mellitus or other causes of secondary CAD. Exclusion criteria also comprised gastrointestinal interventions and antibiotic/prebiotic/probiotic use within the last month and inability to perform a SIBO breath testing. Upon admission, in order to prepare for the breath testing, patients were instructed not to use any laxatives, purgatives, enema or promotility drugs 3 days before testing, not to consume sugary foods/drinks and carbonated water 24 hours before, to practice overnight fasting (except for water) and avoid smoking on the day of breath testing, and not to engage in intense physical activity or use dental adhesives 2 hours prior to the procedure.

In addition to the clinical assessment and paraclinical tests previously mentioned, the patients were subjected to a glucose breath testing and the exhaled gases were measured.

Small intestinal bacterial overgrowth was defined as follows:

- H_2-SIBO: a H_2 rise of $\geq$ 20 parts per million (ppm) over baseline anytime during testing; two peaks were not required for the diagnosis of H_2-SIBO;
- CH_4-SIBO: a CH_4 level of $\geq$ 10 ppm anytime during testing, including at baseline.

Results

We enrolled 41 patients with PD and HBP, without diabetes mellitus or other secondary causes of autonomic dysfunction, who were able to deliver at least 3 breath samples during breath testing.

Both H_2-SIBO and CH_4-SIBO were significantly associated with various PD clinical manifestations as well as disease severity indexes. Patients with H_2-SIBO had higher NMSQ scores than those without H_2-SIBO; they were more susceptible to an akinetic rigid phenotype, xerostomia and neurogenic OH; patients with delayed on and weight loss had significantly higher levels of exhaled H_2 at 30 min after glucose ingestion than their peers. Patients with CH_4-SIBO had shorter OFF time duration and lower Hamilton Anxiety Rating Scale (HAM-A) and Patient Health Questionnaire (PHQ-9) scores than those without CH_4-SIBO; patients without CH_4-SIBO were more susceptible to depression and weight loss, whereas those with CH_4-SIBO were more prone to have cognitive decline, neurogenic OH, and polyneuropathy; basal levels of CH_4 were significantly and positively associated with age and degree of cognitive decline ; patients with delayed on, unpredictable off, no on, freezing of gait (FOG) and weight loss had significantly lower levels of CH_4 at 90 min than those without these features.

Conclusion

Notably, CH_4-SIBO was inversely associated with severity indexes in PD, suggesting a protective role of CH_4-producing archaea in these patients, possibly facilitating levodopa absorption. Considering the differences we found between CH_4-SIBO and H_2-SIBO, we advocate for assessing and analyzing them separately in PD patients, as previously suggested by Dănău et al. [66]. As a matter of fact, archaea behave quite differently from bacteria in relation to disease and intestinal homeostasis [67]. Moreover, provided that SIBO is (positively or negatively, depending on its type) associated with a more severe clinical course in patients with PD and HBP in a gradient dependent manner, we also advocate for a quantitative assessment of the exhaled gases.

10. Conclusions and Personal Contributions

We performed a thorough analysis of the interactions between PD +/- CAD, HBP and intestinal milieu (by interrogation of SIBO and intestinal inflammation/permeability and bacterial translocation) in a cross-sectional manner, emphasizing a facet of the gut-brain-heart axis that has not been described before (Figure 10.1.).

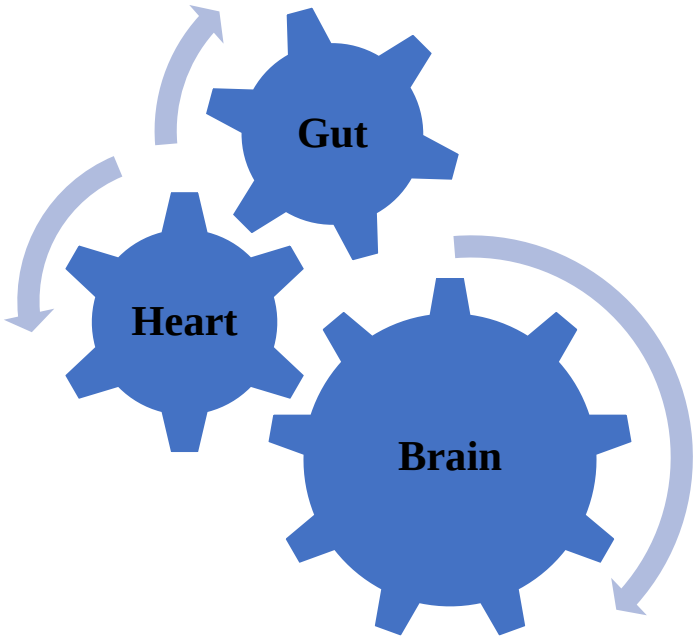

Figure 10.1. The gut-brain-heart axis

We feel that the results generated in our study could lead to new hypotheses and future directions that could warrant study in PD patients with HBP +/- CAD. Larger longitudinal studies focusing on patients with hypertension and PD-related neurogenic OH are required in order to better understand their interactions and to provide therapeutic solutions.

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List of Publications

1. **Tulbă D**, Tănăsoiu AC, Constantinescu A-M, Blidaru N, Buzea A, Băicuș C, Dumitrescu L, Davidescu EI, Popescu BO. Cardiovascular Dysautonomia in Patients with Parkinson's Disease and Hypertension: A Cross-Sectional Pilot Study. Journal of Clinical Medicine. 14(7):2025. 2025; IF: 3.0; https://doi.org/10.3390/jcm14072225

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