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**DOCTORAL THESIS
ABSTRACT**

**DIGESTIVE SYMPTOMS ON
PARKINSON'S DISEASE
PATIENTS**

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Key words: Parkinson's disease, digestive dysfunction, advanced therapies

STATE OF KNOWLEDGE

Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder. It is characterized by bradikinesia, muscle rigidity and resting tremor. Primary described with the motor symptoms, in the last period of time this concept has changed and PD is a non-motor disease as much as a motor disease.(1)

Epidemiology

PD is the second most common neurodegenerative disease after Alzheimer's disease. This mainly affects patients over 60 years. (2) The most risk representative factors are: family history of PD, genetic mutations, exposure to insecticides. Smoking, caffeine intake and exercise are considerate to be protective factors.(3)

Pathophysiology

The most representative pathophysiological change is the loss of dopaminergic neurons in the black matter and the basal ganglia.(4) Only after compensatory mechanisms have been defeated and 60-80% of dopaminergic neurons were destroyed, the motor symptoms such as bradykinesia, muscle rigidity appear. Most of the remaining neurons exhibit eosinophilic inclusions with peripheral halo called Lewy bodies.(5) Like Lewy bodies in the central nervous system, structurally identical inclusions were discovered in the

Auerbach and Meissner plexus. Therefore, a hypothesis was issued that the enteric nervous system is involved in the initiation of BP pathology by retrograde propagation through vagal nerve pathway to the central nervous system.(6)

Clinical manifestations in BP

The cardinal clinical manifestations are bradykinesia, muscle rigidity and resting tremor.

Non-motor symptoms, increasingly studied in the last period, are: cognitive dysfunction, dementia, psychosis, hallucinations, mood and sleep disorders, fatigue, autonomic, olfactory and gastrointestinal dysfunction, pain, sensory disorders, skin manifestations (seborrhea), rhinorrhea.

Digestive manifestations

Digestive manifestations include drooling, dysphagia, taste changes, gastric emptying disorders, weight loss, constipation, defecation disorders. These represent both motor and non-motor components.(7)

Positive and differential diagnosis

The PD diagnosis is based on its distinct clinical features drawn from history and neurological examination. At least bradykinesia and tremor or rigidity must be present to consider the diagnosis of PD. Determining that PD is the cause of motor parkinsonism requires the presence of supportive criteria. To counterbalance the presence of any "red flags" and requires the absence of absolute exclusion criteria.

The clinical diagnosis of PD is established using MDS (Movement Disorder Society) criteria of diagnosis for Parkinson's disease.(8)

Differential diagnosis is made with Lewy body dementia (DLB), corticobasal degeneration (CBD), multisystem atrophy (MSA) and progressive supranuclear paralysis (PSP).

Treatment

Until now, no treatment has been discovered that has an impact on the evolution of the disease. Levodopa is considered the gold standard for symptomatic treatment of BP. There are several types of treatment for these patients such as: pharmaceutical treatment, surgical treatment and non-pharmacological treatment.(9)

PERSONAL CONTRIBUTIONS

The purpose of this project is to evaluate the impact of digestive manifestations on the life of BP patients in order to limit it.

In this way, the disabilities produced by this treatment will be limited as early as possible with the improvement of the quality of life.

It could also have an effect on the life expectancy of these patients, most of who die from associated complications such as aspiration pneumonia due to swallowing disorders.

The main objective is the evaluation of digestive disorders in relation to the form of administration of dopaminergic therapy.

Secondary objectives are:

- Evaluation of digestive manifestations in relation with the stage of the disease.
- Comparison of digestive manifestations with the motor subtypes of the disease
- Assessing the impact of digestive manifestations on quality of life.

MATERIAL AND METHOD

The study base consisted of a group of 109 patients with clinically diagnosed Parkinson's Disease, evaluated during 2017-2019. We conducted a prospective study that included patients admitted to the Clinical Hospital of Neuropsychiatry in Craiova during the period 2017-2019.

Patients were divided into two groups according to the form of medication administration. Thereby:

- I group was formed of patients treated with oral dopaminergic medication
- II group was composed of patients treated with levodopa / carbidopa with continuous intra-jejunal administration

The evaluation parameters

The parameters considered for study are divided into the following categories:

Descriptive parameters:

- Sex
- Age
- Environment
- Clinical diagnoses on admission

Parameters associated with the disease:

- Age at the onset of symptomatology
- Secondary diagnostics
- Administered medication
- Assessment scales performed by the examining doctor
- Evaluation questionnaires completed by the patient

RESULTS

Collected data were included in a database by entering all the parameters mentioned above to make the evaluation of the results possible.

Descriptive analysis

The analysis of the patients included in the study shows that the general predisposition is maintained in this case, therefore, the men represent the majority percentage when evaluating the gender distribution of the patients with BP.

In our study, 69 male and 40 female patients were included.

From the point of view of the environment we can appreciate a slight predominance of the patients from the rural area, with a number of 57 patients who live in the rural area and 52 in the urban area.

From the point of view of the category of digestive manifestations, the patients analyzed had an increased prevalence of constipation followed closely by the loss or change of taste and hypersalivation.

The degree of disability measured using the Schwab and England scale in the patients studied was between 10 and 100% with a mean of 53.21 and a standard deviation of 24.49 percent.

Correlations and comparisons

In this chapter we analyzed the possible links between the different manifestations of BP in the patients studied.

The patients enrolled in the study were divided into several groups for the statistical analysis.

Therefore, the general group includes all patients indifferent of the form of administration of dopaminergic medication, I group included patients undergoing oral medication and II group those treated with Levodopa/carbidopa intestinal gel.

Therefore, the general group consisting of 109 patients was divided in two, group I with a number of 75 patients and the second group with 34 patients.

The age distribution of the patients shows an almost identical resemblance between the general group and the patients treated with oral medication, while the patients treated with intravenous medication have a lower age range, with an average below the previous groups.

The distribution changes with the symptoms onset age. Therefore, in group I the patients were older at the beginning of symptoms as opposed to group II where the age at disease onset decreases to 38 years.

This could be a risk factor for the need for intrajejunal medication and implicitly for the increased prevalence of digestive disorders in these patients.

Disease type distribution revealed different prevalence within the 3 groups.

While in the general group the temor-dominant type predominated followed closely by the one with postural instability, in the other two groups there were major differences.

The patients in group I had a predominance of the temor-dominant form, preceded by the rigid-akinetic form, but the patients treated with L-dopa / carbidopa intestinal gel had a diametrically opposite distribution compared to the previous group.

This fact could prove the predominance of digestive symptoms in patients with BP in the postural instability form.

Correlations between digestive symptoms and Hoehn & Yahr stage

Comparison of the digestive symptoms domain in the NMSQ questionnaire with the stage of the disease analyzed with the Hoehn & Yahr staging scale in the general group showed a positive correlation with a strong statistical significance with $p < 0.001$.

The analysis of the frequency of digestive disorders of BP in relation to the evolution of the disease, expressed by Hoehn & Yahr staging, shows an increased prevalence of constipation in all stages of the disease, followed by hypersalivation, taste change, incomplete defecation, gastroparesis disorders such as nausea, vomiting.

The most frequent manifestations were incontinence for fecal matter, present only in the stage 3 and 5 of the disease, in our study.

In group I, the connection between the digestive symptoms and the stage of the disease was maintained. They presented with a positive correlation, with a statistical significance with $p < 0.001$.

In lot II there was a positive correlation between the digestive manifestations and the H&Y stage, but this time there was no statistical significance ($p = 0.051$).

Correlations between NMSQ and Hoehn & Yahr stage

We note the presence of a connection between them and the BP stage determined with Hoehn & Yahr staging scale.

Therefore we can see below the presence of a positive correlation between NMSQ and the H&Y stage, with a statistical significance with p below 0.001.

This fact points out that as the disease progresses, the non-motor symptoms increase.

In the analysis of lot I we observe the maintenance of the same tendency as in the general overlying group, presenting a positive correlation with a strong statistical significance ($p < 0.001$).

On the other part, in the analysis of lot II the situation changes, between the stage of the disease and the non-motor manifestations there is no statistical significance correlation.

Correlations between NMSQ and UPDRS motor

For a clearer picture of the relationship between motor and non-motor manifestations, resulting from the analysis of patient data included in this study, we made correlations between the non-motor domains of the NMSQ questionnaire and the motor symptoms evaluated by the UPDRS score.

We can see in the table below that not all NMSQ domains showed a positive statistical significant correlation with the UPDRS score.

The gastrointestinal and sleep disorders showed the strongest correlation with motor manifestations.

These were followed by the gastrointestinal disorders, various disorders, hallucinations and memory disorders.

On the other part, urinary disorders, depressive disorders and sexual disorders did not show statistically significant correlations with motor symptoms.

Correlations between digestive symptoms and motor UPDRS

When we compare the digestive symptoms with the motor manifestations of BP in the general group, we observe a close connection between them with a positive correlation and a strong statistical significance with $p < 0.001$

The positive correlation between digestive symptoms and motor UPDRS is also maintained in the case of group I with a strong statistical significance with $p < 0.001$

In the II lot the analysis of the digestive symptoms in comparison with the motor manifestations shows us that the intrajejunal medication could change the intensity of the motor manifestations, not being related with the evolution of the digestive symptoms. In this case, there is no correlation between the two.

Correlations between UPDRS motor and PDSS

The analysis of the sleep disorders in relation with the associated motor manifestations showed negative correlations in the patients treated with oral medication, but the patients treated with dopaminergic therapy with intrajejunal administration did not have an interrelation between the PDSS and UPDRS motor scores.

Correlations between UPDRS motor and MMSE

The comparative analysis of the cognitive disorders in relation with the motor symptoms showed an interrelation between them in the case of the general group and of the patients treated with oral dopaminergic therapy.

At the same time, patients in group II no longer have the same tendency, which could indicate that continuous administration of L-dopa / carbidopa intestinal gel may influence cognitive disorders.

We mention that in this study were not included patients with major cognitive deficiency because it presented an impediment to the application of the battery of tests if the patients were not able to self-assess their condition.

Correlations between NMSQ and PDQ-8

The analysis of the relationship between non-motor manifestations and quality of life revealed a positive interrelation in the general group, in I and II group.

This fact shows the importance of detailed evaluation of non-motor manifestations because of their major impact on the quality of life of BP patients.

Correlations between digestive symptoms and PDQ8

The analysis of the influence of digestive symptoms on the quality of life within the general group showed a positive correlation with $p < 0.001$ statistically significant.

The same tendency was maintained for patients treated with oral medication, showing the effect of digestive manifestations on the quality of life of these patients with a positive correlation between digestive symptoms and PDQ-8 with $p < 0.001$.

For group II, the positive correlation was maintained with a strong statistical significance $p = 0.001$, despite the smaller number of patients.

CONCLUSIONS

Patients with BP present numerous non-motor manifestations beside the motor manifestations associated with the disease.

The interrelation between them determines the decrease of the quality of life both by the functional limitations determined by the motor manifestations and by the disturbance of the social life imposed by non-motor manifestations.

The analysis of the relationship between age at onset of symptomatology and the type of medication needed, led to the conclusion that patients presenting with the first symptoms at a younger age have an increased susceptibility to require advanced therapies later in the course of the disease.

Therefore, the study of digestive manifestations in patients with BP showed the importance of early diagnosis of gastrointestinal symptoms, this fact influence the management of the patient with BP.

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