PHD THESIS

SENSITIVE-SENSORIAL AND VEGETATIVE DISTORTIONS IN PARKINSON'S DISEASE

SCIENTIFIC COORDINATOR – PhD Professor Marcel Pereanu

PhD STUDENT – Liliana Cuibus

SUMMARY

A. Generalities.

Parkinson's is a neurovegetative disease caused by the loss of dopaminergic neurons in the black matter, as well as in other dopaminergic and non-dopaminergic areas at brain level.

Current research has revealed a multitude of non-motor signs and symptoms, such as vegetative symptoms, sensitive-sensorial dysfunctions, sleep disorders, cognitive disruptions, behavioral disruptions. These non-motor issues can precede motor signs and symptoms and require adequate treatment.

The evaluation of the sensitive-sensorial and vegetative disorders since the early stages of Parkinson is the object of the hereby research paper.

Sensitive-sensorial disruptions have been described in numerous clinical studies since the incipient stages of Parkinson's disease. Non-motor symptoms have been described for the first time by Trousseau and Charcot in the 19th century.

Parkinson's is a disorder with progressive aggravation, corresponding with the loss of dopaminergic neurons in the black matter.

Prevalence – 102 - 190 cases for every 100,000 people.

Incidence per sexes is 2.14/1 in favor of men.

Parkinson's starts many years before its actual clinical debut, through non-motor symptoms. The evolution is continuous for 15 – 25 years, and the evolution of the disease is variable from one patient to another.

Non-motor signs and symptoms in the Parkinson's disease.

Both the dysfunction of the autonomous nervous system and the sensitive-sensorial disruptions are part of the non-motor, non-dopaminergic disruptions.

Digestive disruptions:

Constipation.

Data from the literature shows 58% of the Parkinson's patients suffer from constipation.

Involvement of the enteric neurons proven by the presence of the Lewy corpuscles at the colon's myenteric plexus.

Sialorrhea.

This symptom is common for 78% of Parkinson patients. Hypersalivation and saliva running down the face can cause mouth ulcerations.

Uro-genital dysfunction.

Nycturia is the most precocious sign of autonomous dysfunction. It is often followed by the rise in miction frequency and the need for urgent miction, then difficult miction.

Sexual dysfunction.

This dysfunction is a common problem with Parkinson's patients. It appears as an initial dysfunction of the autonomous nervous system, before the appearance of motor symptoms.

Hyper sexuality has been reported especially with patients who undergo agonist dopaminergic treatment, and require a diminishing of the agonist dosage.

Heart system dysfunctions – orthostatic hypotension.

Most frequent in the late stages of Parkinson's and can be aggravated by dopaminergic therapy.

Orthostatic hypotension appears after the decreasing vasoconstriction after sympathetic stimulation.

Thermo-regulation and sudoration dysfunctions.

Over 64% of Parkinson's patients were noted to have Lewy corpuscles and cellular loss in the hypothalamus. Sudoration growth is more accentuated at the head, face and body, and compensates for the decrease of sympathetic activity at the extremities.

Sensitive-sensorial dysfunctions.

a) Olfactory dysfunction.

Most Parkinson's patients present olfactory dysfunction – 90%. Detection of the dysfunction can be a screening method for patients at risk of Parkinson's.

b) Pain and dysesthesia.

Patients complain of various pain sensations, such as muscle stretch, tension, diffuse pain, neuralgic pain, burns.

Sensory symptoms have been frequent especially with patients with motor fluctuations in off periods and need to be differentiated from the painful dystonic spasm which appears in the morning.

B. The special part.

The objects of this study are:

- The presence of sensitive-sensorial and vegetative dysfunctions in various stages of evolution of Parkinson's disease;
- Existence of association between sensitive-sensorial and vegetative symptoms at the studied lot;
- Highlighting the correlations between vegetative and sensitive-sensorial symptoms at the studied lot;
- Highlighting the presence of sensitive-sensorial and vegetative symptoms since the first stage of Parkinson's.

Material and method.

The study was carried out over 200 patients recruited from the ambulatory and the neurology section of the Sibiu Clinic County Hospital.

The hereby study is prospective, observational and descriptive. The patients' recruitment period lasted between December 2007 and June 2011. Patients were aged 55-75. Patients in the study lot originate from both urban and rural environments.

The data processing solution we employed was SPSS (Statistic Program for Social Science), version 10, which enabled us to statistically analyze the data and transfer it into graphic representations.

With instruments specific to advanced statistics, SPSS allows problems to be solved by offering solutions that can lead to better knowledge of the investigated phenomena thus endorsing the decisions' substantiation process.

Criteria for inclusion into and exclusion from the study.

Inclusion criteria:

- Patients diagnosed with Parkinson's after the neurologic exam and paraclinic investigations;
- Patients in various stages of evolution according to the Hoehn-Yahr classification:
  - ✓ stage I – unilateral affliction;
  - ✓ stage II – unilateral affliction without postural dysfunctions;
  - ✓ stage III – bilateral affliction with slight postural unbalance (patient leads normal life);
  - ✓ stage IV – bilateral affliction with postural instability (patient requires support for daily activities).
- Cranial CT exam – normal.

Exclusion criteria:

- Patients who suffer from sugar diabetes type I, II, due to the possibilities of presenting false positive results;
- Patients with Parkinson's in the V Hoehn-Yahr stage;
- Patients with associated cardiovascular, genital-urinary and digestive dysfunctions;
- Patients aged below 55 or over 75;
- Patients who had encephalitis, cranium-cerebral trauma in pathologic personal antecedents;
- Patients who display cerebellar signs, crisis oculogira, over-nuclei paralysis of the gaze in the clinic picture.
- Patients who responded negatively to adequate L-Dopa dosage.

Following the statistical analysis of the data and the interpretation of possible association and correlation, the theme of the research engendered several discussions:

The statistical analysis of the data was performed using the Statistic Program Social Science program, version 10. We used Chi-Square and the binomial tests. Results obtained with the Chi-Square test gave us the answer to the question whether two variables were associated, namely if the appearance of a level of the first variable favored the appearance of certain levels of the other variable and vice versa.

The pool of patients contained 40% female patients and 60% male. The number of male patients was significantly higher than that of female, causing a *p* index with statistical significance ($p<0.05$).

Patients in the I and II, III, respectively IV stages were to a greater extent within the 66-75 years age category (59%, 58%, 80% respectively) against the 55-65 year segment (41%, 43%, 20% respectively).

The percentage of patients from the urban environment was predominantly greater than rural patients.

There was no significant association between the age of the patients and the evolution of the disease ($p=0.407>0.05$).

The percentage of patients with olfactory dysfunction was 80% in both age groups.

As for pain, the percentage of patients who experienced it was roughly similar, 45% for both age groups, as stated in the literature.

Patients who complained of slight pain accounted for 73% at the 66-75 year age group and 27% at the 55-65 year age group.

Intestinal dysfunctions with defecation rate rarer than three days were common for 43-57% of the patients. Data in the literature read about intestinal dysfunctions at a rate of 38-55%.

Sexual dysfunctions (erectile and ejaculation dysfunction, hyper-sexuality) occurred for 35-65% of the lot, which is common to Parkinson's patients.

Data analyzed statistically revealed that urinary dysfunction was common for 36-47% of the patients in the lot, irrespective of the age group. Nycturia was the most precocious sign of autonomous dysfunction according to the data in the literature.

Patients who complained of sudoration disorders, nocturnal or diurnal, accounted for 44-46%. Over 64% of the Parkinson's patients displayed excessive sudoration of the head, face and torso, as a consequence to the loss of the Lewy corpuscles and cellular loss in the hypothalamus. Excessive sudoration can appear during the off periods at patients with motor fluctuations.

Permanent salivation disorders were discovered not only at patients aged 66-75 years, and intermittent salivation disorders were common for 48-52% of them.

In the studied lot no patients displayed permanent deglutition problems at the 55-65 year age group.

Orthostatic hypotension as main manifestation of the dysfunction of the autonomous cardiovascular system was present at 75% of the patients aged 66-75, and at 25% of the patients aged 55-65. The prevalence of orthostatic hypotension in specialty studies was 30-50%, most often accompanied by olfactory system dysfunction.

More than four non-motor dysfunctions resulted for 62% of the patients aged between 66-75 years and 40% of the patients aged between 55-65. Male patients with smelling problems (average – 67% - and severe hyposmia – 70%) were significantly more numerous than that of female patients (33% and 30%). In exchange, 60% of the female patients suffered from anosmia against 40% of male patients, results similar to the literature's.

Pain of various intensity occurred in 44% of the male patients and 48% of the female patients.

We cannot associate a statistical correlation between the sex of the patients in the studied lot and intestinal dysfunctions, although 28-33% of the patients presented this non-motor dysfunction, similar to the data in the literature.

80% of the male patients presented sexual dysfunctions, while female patients only accounted for 20%, resulting a *p* index statistically significant ($p = 0.004 < 0.05$). In a clinic study run on the 21 men with Parkinson's, 17 presented erectile dysfunction. The main problem was getting and keeping an erection going.

Same as in the case of sexual dysfunctions, the percentage of male patients (70%) with urinary issues was significantly greater than that of female patients' (30%), determining a statistically significant *p* index.

Sudoration problems were present in approximately equal percentage for both sexes (45%). Sialorrhoea was present for 29-31% for both sexes.

Irrespective of the patient's sex, the percentage of those with several non-motor associated dysfunctions ranged between 55-67%.

The percentage of patients with cardiovascular problems was 50% for both male and female patients.

Patients in stages I, II Hoehn-Yahr presented olfactory afflictions in a percentage of 83%. 60-80% of the patients in all four stages of evolution of Parkinson present smelling disorders, as read the literature [49], [50], [51]. Literature was nonetheless unable to establish a link between the severity of the disease and that of the olfactory disorder.

In stages I, II, 44% of the patients experienced pain, in stage III 43% and 70% in stage IV. In the literature, clinic surveys showed 50% of the patients experienced pain.

Irrespective of the evolution of the disease, 49-55% of the patients presented urinary disorders.

Sudoration dysfunctions occurred in the first stage of the disease; in stage IV nocturnal sudoration was common for 40% of the patients. Data in the literature mentioned sudoration as a non-motor sign of Parkinson to 64% of the patients.

The percentage of patients who showed deglutition-related problems was 20%, although data in the literature mentioned something around 50-60%.

None of the patients in stage I, II or III Heohn-Yahr of the 200 presented orthostatic hypotension, but 40% of the patients in stage IV presented the same non-motor dysfunction.

76% of the patients with intestinal transit disorders, 90% of the patients with sexual dysfunctions, 80% of the patients with urinary dysfunctions, 70-80% of patients with sudoration problems, 80-85% of patients with salivation problems, 60-84% of the patients with deglutition problems and 83-90% of the patients with pain complained of olfactory disorders.

52% of the patients with intestinal transit disorders, 48% of the patients with sexual dysfunctions, 46% of the patients with urinary dysfunctions, 49-53% of patients with sudoration problems, 48-60% of patients with salivation problems, 27-50% of the patients with deglutition problems and 75% of the patients with cardiovascular disorders experienced pain.

Statistical analysis revealed the following statistically significant correlations with a $p<0.05$ index between various non-motor symptoms:

- Olfactory dysfunction and intestinal transit disorder;
- Urinary disorder and sexual disorders;
- Dysphagia and smelling disorders;
- Salivation and sudoration disorders;
- Smell and number of non-motor disorders;
- Intestinal transit issues and number non-motor disorders;
- Sudoration and intestinal transit disorders;
- Pain and salivation dysfunctions;
- Sudoration disorders and pain.

We reached a number of 23 final conclusions, as follows:

1. Of the studied lot, 75% of the patients were in stage I, II Hoehn-Yahr, 20% of the patients were in stage III Hoehn-Yahr, and 5% in stage IV.
2. In the study, 40% of the patients were female and 60% are male.
3. Of the 200 patients, 65% lived in urban and 35% in rural environments.
4. Patients in stages I, II Hoehn-Yahr, stage III, respectively stage IV were to a greater extent in the 66-75 year age segment (59%, 58%, and 80% respectively) against patients in the 55-65 year age segment (41%, 42%, and 20% respectively).
5. Of sensitive-sensorial disorders, pain varied in intensity for 45% of the patients.

6. According to the Hoehn-Yahr classification, in stages I, II 44% of the patients experienced pain (16% mild pain, 11% average pain, 17% severe pain), in stage III 42.5% experienced pain (12.5% mild, 10% average, 20% severe) and in stage IV, 70% did so (10% slight, 60% severe).
7. Pain was common to patients with olfactory dysfunction in various degrees of intensity, as follows: 83% slight pain, 90% average and 85% severe.
8. 45-60% of the patients with gastrointestinal, sexual and urinary, sudoration, salivation disorders experienced pain, except for patients with cardiovascular disorders, where the percentage was 75%, and patients with deglutition issues, where the percentage ranged between 27-50%.
9. In stages I, II, 83% of the patients' sense of smell has been affected, in stage III 70% of the patients' sense of smell has been affected, and in stage IV 60% of the patients' sense of smell has been affected. There is no direct correlation between the smell affliction and the disease' severity.
10. Dysfunction to olfactory system – hyposmia – was statistically determined for 70% of male patients, while anosmia was revealed for 60% of the female patients.
11. Olfactory dysfunction in various degrees occurred to patients with pain, as follows: 50% slight, 49% average, 48% severe hyposmia, 45% anosmia.
12. Olfactory dysfunction was present for patients in the lot who experienced pain at a rate of 45-50%; pain was present in between 80 and 90% of the patients with olfactory dysfunction.
13. Between 77 and 90% of patients with gastrointestinal, genital-urinary, sudoration, salivation dysfunctions also suffered from olfactory dysfunctions, except for patients with permanent deglutition problems, where the percentage was 60%.
14. Gastrointestinal disorders occurred for 30% of the studied lot, and split per age segments they occurred to 43% of the patients aged 55-65 and to 57% of the patients aged 66-75.
15. In stages I, II 48% of the patients and 50% of the patients in stage IV suffered from urinary disorders.
16. Genital dysfunction was present for just 20% of the patients.
17. Between 18-32.5% of the patients in the lot presented salivation disorders: 2.5% were permanent and 30% were intermittent, while in stages I, II Hoehn-Yahr 34% and 40% in stage IV of the patients have salivation disorders.

18. Deglutition disorders were present for 14.5% of the patients in the lot: 5% were permanent and 9.5% intermittent, with 34% of the patients in stage I, II Hoehn-Yahr and 40% in stage IV.
19. Orthostatic hypotension was present to just 2% of the studied lot, while in stage IV Hoehn-Yahr it was present to just 40% of the patients.
20. Statistics revealed over 62% of the patients had more than three associated non-motor disorders, but no patient in the lot had all of them.
21. Non-motor symptoms, such as: gastrointestinal, genital-urinary, sudoration, salivation, orthostatic hypotension were more frequent with age and occurred since the stage I of Parkinson's, according to the Hoehn-Yahr classification.
22. Following the statistical analysis of the data, these non-motor symptoms existed before the Parkinson diagnostic.
23. Dysfunction to the olfactory system, constipation, chronic pain, genital-urinary and cardiovascular disorders, next to Parkinson positive family history could become associated in a risk scoring in the premotor stage of Parkinson's.

This paper's innovation factor consists in:

- The approach of Parkinson patient in the initial stages of the illness immediately after the setting of the diagnostic
- The research of non-motor sensitive-sensorial and vegetative disorders before they become the object of the patient's symptoms

The study included a great number of patients (200), and the statistical analysis of the data, next to the complexity of the examination offered us an integrated image on the associations and correlations of various sensitive-sensorial and autonomous disorders, as well as their presence since the incipient stages of the Parkinson's disease.

Another particularity revealed by the study consists of discovering the connection between the severity of the illness and the severity of the affliction of the olfactory function, respectively the intensity and occurrence of pain.

The presence of several non-motor dysfunctions as of stage I, statistically proven at the studied lot, represents a major contribution which proves these non-motor symptoms occur with patients with Parkinson's before the diagnostic.

Approaching the patients with Parkinson’s disease is an extremely complex endeavor, and the precocious presence of the non-motor symptoms before the motor symptoms needs to be acknowledged and identified by the physician.