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Gastrointestinal Dysfunction in Parkinson's Disease

Neurology

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ABSTRACT

Background: Parkinson's disease (PD) is an incurable multisystem condition that causes enormous morbidity and costs in healthcare. The most frequent non-motor symptoms (NMS) manifestations of PD are gastrointestinal (GI) dysfunctions, which affect roughly 65% of people.
Aim of The Work: To define the frequency of GI symptoms in PD (both treated and untreated), and to correlate the existence or lack of GI symptoms with stages of the disease.
Patients and Methods: From February 2021 to August 2021, this case research was carried out in tertiary care at Al-Azhar University Hospitals Al-Hussein and Sayed Galal on a total of 120 subjects, divided into 60 Parkinson's disease patients and a matching group of healthy individuals.
Results: This study showed that upper gastrointestinal tract dysfunction, which has been evaluated by the Leeds dyspepsia questionnaire, and lower gastrointestinal tract dysfunction, which was assessed by the Cleveland Constipation Score and Rome-IV criteria, had a highly significant difference between PD and the healthy control group.
Conclusion: The most common gastrointestinal premotor symptoms of Parkinson's disease were constipation and defecatory dysfunctions.

Keywords: *Gastrointestinal Dysfunction; Parkinson's Disease; Non-Motor Symptoms.*

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INTRODUCTION

Constipation, bloating, drooling, dysphagia, vomiting, nausea, and gastroparesis are frequent GI symptoms in individuals with PD, and they can appear up to 20 years before motor symptoms appear. GI symptoms appear throughout the disease course and affect the entire length of the GI tract [1].

Several neuropathological investigations have identified early accumulation of Lewy bodies (LB) in the Enteric Nervous System (ENS) and dorsal motor nucleus of the vagus, which is consistent with clinico-epidemiological data. These findings are related to the severity of motor and gastrointestinal symptoms, and they reflect impaired intestinal peristalsis / motility, vagal dysfunction, modified intestinal permeability, GI tract sensory impairments, and medication side effects, all of which can contribute to GI dysfunction in PD [2].

In people with PD, aspiration pneumonia, intestinal perforation, intestinal obstruction, megacolon, and malnutrition are all common causes of hospitalization [(1).] Constipation is thought to be caused by a combination of delayed GI transit and paradoxical voluntary sphincter contractions during faeces. Constipation severity was linked to a quicker progression of cognitive and motor diseases, as well as a negative influence on quality of life [3].

Management for GI dysfunction in Parkinson's disease is typically ineffective and compounded by side effects [(4)]. Gastroparesis and delayed intestinal absorption might have a negative influence on the treatment, resulting in irregular levodopa uptake and motor swings [5].

Recent studies have revealed that the microbiota-gut-brain-axis, or bidirectional connection between the gut and the brain, may have an even greater impact on GI dysfunction, PD pathogenicity, and levodopa metabolism. [6]

The current study aimed to define the prevalence of gastrointestinal tract symptoms in Parkinson's disease (PD) (both treated and untreated), and to correlate the existence or lack of GI symptoms with the stages of the disease.

PATIENTS AND METHODS

From February 2021 to August 2021, this case research was carried out in tertiary care at Al-Azhar University Hospitals Al-Hussein and Sayed Galal on a total of 120 subjects, divided into 60 PD patients and a matched group of healthy controls.

Inclusion criteria:

Patients over the age of 18 with a clinical diagnosis of idiopathic Parkinson's disease based on the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria were enrolled [7]. A matched group of healthy control was also enrolled: They were over the age of 18 and had no clinical manifestations of Parkinson's disease (a partner, sibling, or child who shares their PD patient's dietary habits).

Exclusion criteria:

Patients with secondary Parkinsonism, tube-fed patients, medical or surgical events that prevent data gathering questionnaires from being completed and inability to offer consent indicating significant cognitive impairment.

Data collection

Patients group:

Sixty patients with Parkinson disease were studied (42 male and 18 female) with a range of age between 44-66 years old. In each patient a grade of the disease was determined. Patients were questioned for autonomic symptoms including GIT symptoms.

Control group:

Sixty healthy control were studied exhibiting no clinical manifestations of PD nor receiving any medications which could affect the autonomic nervous system or causing parkinsonism.

Careful history taking:

Personal history: name, age, sex, residence, occupation, economic status, telephone number, and particular habits of medical significance; complaint: onset, course, and disease duration; history of the present illness (clinical manifestation of PD and associated autonomic manifestations, particularly GIT symptoms), Review of other systems: endocrine, cardiovascular system (CVS), respiratory, genitourinary, musculoskeletal and skin and past history of chronic diseases, drug intake, surgical operation or blood transfusion, Family history, current medications, Investigations and assessment:

Organic causes of dyspepsia and constipation were excluded by careful history-taking, physical examination, laboratory tests, and endoscopic procedures. Patients older than 50 years were subjected to upper gastrointestinal endoscopy if they had dyspepsia and lower gastrointestinal endoscopy if they had constipation. All dyspeptic patients younger than 50 years were tested for Helicobacter pylori stool antigen, amylase, and lipase, and had an abdominal ultrasound. All constipated patients younger than 50 years were tested for thyroid function, fecal occult blood, and had a local per rectal examination in addition to the above-mentioned investigations. All patients were reviewed by a consultant gastroenterologist to exclude any organic causes before enrollment in the study.

At recruitment, patients completed self-administered questionnaires and provided a blood sample. Liver function tests (Serum Alanin transeferase (ALT), Serum Aspartate transferase (AST), Serum Albumin), glycaemic profiles (Fasting blood glucose level (FBS), HBA1c), lipid profiles (total serum cholesterol, Serum triglyceride level (TG), High density lipoprotein (HDL), Low density lipoprotein (LDL), erythrocyte sedimentation rate (ESR), and CRP.

To assess the severity of Parkinson's disease, the modified Hoehn and Yahr [8] staging system has been used.

The Leeds Dyspepsia Questionnaire (LDQ) has been utilized to evaluate upper gastrointestinal symptoms in patients [10].

Constipation severity and gut motility have been assessed using Cleveland Constipation Score(CCS) [12].

Ethical Approval

The research was accepted by our faculty's ethical committee, and patients and controls gave their informed written consent.

Statistical analysis of the data

The data entered into the computer was examined by employing the IBM SPSS software program version 20.0. (Armonk, NY: IBM Corp). Qualitative data was represented using percentages and numbers. The Kolmogorov-Smirnov test has been used to validate that the distribution was normal. The terms "range" (min and max), "mean," "standard deviation," "median," and "interquartile range" have been employed to describe quantitative data (IQR). The obtained findings were evaluated at a 5% significance level.

The used tests were:

Mann Whitney test

To compare two investigated groups with abnormally distributed quantitative variables.

Spearman coefficient

To establish a relationship between two abnormally distributed.

RESULTS

Among 60 patients studied, about 42 (70%) were males, and 18 (30%) were females, with a mean age of 55 years (table 1).

Our study showed that there was no significant difference between the studied groups regarding baseline demographics (sex, BMI) except for age, which was statistically higher in the Parkinson's disease group, with no significant difference among the groups regarding smoking, alcohol, and caffeine intake.

According to HY staging, the majority of patients' groups were scored as stages 3 and 4 (table 2).

There was a significant difference between patients and controls as regards upper gastrointestinal symptoms that have been assessed by LDQ (table 3).

The prevalence of constipation was higher in the PD group than in the healthy group (table 4).

There was a positive correlation between HY and both LDQ and CCS (tables 5 , 6).

		Parkinson's Disease (N = 60)		Healthy Control (N = 60)		Stat. test	P-value
Age (years)	Mean ± SD	55.1 ± 6.31		32.9 ± 7.42		MW = 1868.5	< 0.001 HS
	Median	55		31.5			
	Rang	(44-66)		(19 -50)			
Sex	Male	42	70%	41	68.3%	X^2 = 0.039	0.843 NS
	Female	18	30%	19	31.7%		
DM	No	56	93.33%	55	91.7%	X^2 = 0.12	0.729 NS
	Yes	4	6.67%	5	8.3%		
HTN	No	42	70%	57	95%	X^2 = 12.9	< 0.001 HS
	Yes	18	30%	3	5%		
AF	No	54	90%	60	100%	X^2 = 6.3	0.012 S
	Yes	6	10%	0	0%		
BMI (kg/m²)	Mean ± SD	21.17 ± 4.31		23.50 ± 3.43		MW = 1788	0.949 NS
	Median	20		24.00			
	Rang	14-31		18-31			
Smoking	No	53	88.33%	51	85%	X^2 = 0.288	0.591 NS
	Yes	7	11.67%	9	15%		
Alcohol	No	60	100%	60	100%	-----	-----
	Yes	0	0%	0	0%		
Caffeine	No	23	38.33%	24	40%	X^2 = 0.035	0.852 NS
	Yes	37	61.67%	36	60%		

Table 1: Comparison between patients and controls in terms of demographic data

		Parkinson's Disease (N = 60)	Healthy Control (N = 60)	MW	P-value
ALT (U/L)	Mean ± SD	22.35 ± 5.39	21.7 ± 2.57	3633	0.99 NS
	Median	22	22		
	Rang	12 – 39	14 – 25		
AST (U/L)	Mean ± SD	23.12 ± 5.66	22.9 ± 3.23	3660	0.877 NS
	Median	22	22.5		
	Rang	20 – 44	16 – 28		
HbA1C (%)	Mean ± SD	5.11 ± 1.31	5.31 ± 1.39	3768	0.470 NS
	Median	4.75	5		
	Rang	3.5 – 7.5	3.5 - 7.6		
CHOL (mg/dl)	Mean ± SD	199.5 ± 43.84	185.7 ± 38.79	3333	0.12 NS
	Median	200	190		
	Rang	145 – 300	120 – 250		
TG (mg/dl)	Mean ± SD	85.77 ± 18.9	88.27 ± 14.47	3902	0.154 NS
	Median	80	90		
	Rang	50 – 125	50 – 110		
LDL (mg/dl)	Mean ± SD	73.30 ± 22.01	65.20 ± 13.48	3310	0.1 NS
	Median	68	62.5		
	Rang	55 – 150	50 – 100		
HDL (mg/dl)	Mean ± SD	61.50 ± 7.68	60.55± 7.55	3511	0.536 NS
	Median	65.5	60		
	Rang	45 – 78	45- 75		
ESR (mm/h)	Mean ± SD	13.63 ± 2.89	13.62 ± 3.44	3561	0.719 NS
	Median	13	12		
	Rang	10 – 21	11- 21		
CRP (mg/L)	Mean ± SD	3.25 ± 2.45	2.30 ± 1.5	3258	0.06 NS
	Median	2.5	2		
	Rang	1 – 12	1 – 5		

MW: Mann Whitney U test. NS: A p-value > 0.05 is regarded as non-significant.

Table 2: Comparison between patients and controls in terms of laboratory data

This table shows that there are no statistically significant differences (p-value > 0.05) between patients and controls in terms of studied laboratory data (ALT, AST, HbA1C, CHOL, TG, LDL, HDL, ESR, and CRP).

Heohn and Yahr	Parkinson's Disease (N = 60)
Stage I	6 (10.00%)
Stage II	6 (10.00%)
Stage III	28 (46.67%)
Stage IV	20 (33.33%)
Stage V	0(0%)

Table 3: Description of Heohn and Yahr in all studied patients

		Parkinson's Disease (N = 60)		Healthy Control (N = 60)		X^2	P-value
LDQ	Very mild (1-4)	0	0.0%	11	18.33%	69.57	< 0.001 HS
	Mild (5-8)	2	3.33%	27	45. 0%		
	Moderate (9-15)	21	35.0%	22	36.67%		
	Sever (≥ 16)	37	61.67%	0	0.0%		
CCS	Yes	57	95%	9	15.0%	77.6	< 0.001 HS
	No	3	5%	51	85.0%		

X2: Chi-square test. HS: A p-value < 0.001 is regarded as highly significant.

Table 4: Comparison between patients and control as regard CCS and LDQ
This table shows that there are highly statistically significant differences (p-value < 0.001) in the CCS Score between PD and Healthy Control. In terms of LDQ score, there are highly statistically significant differences (p-value < 0.001) between Parkinson's disease and Healthy Control.

	Correlation (r)	P-Value	95% CI for ρ
HY vs Frequency	0.476	0.000	(0.239; 0.659)
HY vs Difficulty	0.400	0.002	(0.153; 0.600)
HY vs Completeness	0.294	0.023	(0.037; 0.514)
HY vs Pain	0.452	0.000	(0.211; 0.641)
HY vs Time	0.373	0.003	(0.123; 0.579)
HY vs Assistance	0.196	0.133	(-0.063; 0.431)
HY vs Failure	0.532	0.000	(0.305; 0.701)
HY vs History	0.543	0.000	(0.319; 0.710)

p-value < 0.05 is considered significant., p-value > 0.05 is considered non-significant.

Table 5: Pairwise Spearman correlations between CCS and Heohn and Yahr in Parkinson's Disease (N=60)

A significant positive correlation between Heohn and Yahr scale and CCS score (r = 0.647, p = 0.000).

	Correlation (r)	P-Value	95% CI for ρ
HY vs Indigestion	0.311	0.016	(0.056; 0.528)
HY vs Heart burn	0.654	0.000	(0.459; 0.789)
HY vs Regurgitation	0.378	0.003	(0.129; 0.583)
HY vs Belching	0.393	0.002	(0.145; 0.595)
HY vs Vomiting	0.585	0.000	(0.370; 0.740)
HY vs Early satiety	0.560	0.000	(0.340; 0.722)
HY vs Dysphagia	0.619	0.000	(0.414; 0.765)
HY vs Nauseas	0.639	0.000	(0.440; 0.778)

p-value < 0.05 is considered significant., p-value > 0.05 is considered non-significant.

Table 6: Pairwise Spearman Correlations between LDQ score and Heohn and Yahr in Parkinson's Disease

A significant positive correlation between Heohn and Yahr scale and LDQ score (r = 0.816, p = 0.000).

DISCUSSION

Parkinson's disease (PD) is a multisystem, incurable illness that generates enormous morbidity and costs in healthcare. The most frequent non-motor symptom (NMS) of PD is GI dysfunction, which affects 65 percent of sufferers and has a major negative influence on life quality. [15]

Constipation, bloating, dysphagia, drooling, vomiting, nausea, as well as gastroparesis are all common gastrointestinal symptoms that can occur up to 20 years prior to motor signs. Symptoms appear throughout the disease's course and impact the entire GI system [16].

The assessment of GI symptoms throughout PD was highlighted as a primary subject of concern since gastrointestinal symptoms are present throughout Parkinson's disease, constitute major conflict, and are frequently related with consequences [15].

In this research, we set out to aim to define the incidence of gastrointestinal tract symptoms in PD and to correlate the presence or absence of gastrointestinal tract symptoms with the stages of the disease.

From February 2021 to August 2021, this case research was carried out in tertiary care at Al-Azhar University Hospitals Al-Hussein and Sayed Galal on a total of 120 subjects, divided into 60 Parkinson's disease patients and a matched group of healthy controls.

During this study, 144 subjects were assessed for eligibility, and 120 subjects were involved in the study (60 in each group). Of all the eligible patients, 20 patients were excluded from the study based on the inclusion criteria, and 4 patients refused to take part in the research.

Ultimately, the analysis relied on the data of 120 subjects who were divided into 60 PD patients and 60 healthy control groups.

The current research shows that there were no significant differences between the studied groups concerning baseline demographics (sex, BMI) except for age, which was statistically significantly higher in

the Parkinson's disease group (p values > 0.001), with no significant differences among the groups concerning smoking, alcohol, and caffeine intake.

Lubomski et al. [15] performed a comparative study on 103 patients with PD and 81 control persons, with results gathered from verified questionnaires including severity of constipation, upper and lower GI symptoms, and physical activity to assess the GI symptoms in patients with PD with an effect on patients' quality of life, and found that there had been a significant difference between the two groups with respect to age (p = 0.023) and GI symptoms severity (p = 0.023). In addition, they found that PD participants reported a much lower daily caffeine intake (p = 0.003) and a significantly lower rate of alcohol consumption (p = 0.003) than the healthy control group, which contradicts our findings.

A prospective study was conducted by Cersosimo et al. [17] on 129 Parkinson's disease patients and 120 healthy controls who completed a standardized questionnaire to evaluate the prevalence of gastrointestinal symptoms (GIS) in PD patients compared to healthy controls, as well as their time of onset in connection to motor symptoms. They discovered that age and gender were not substantially associated among PD patients and control volunteers, contrary to our findings.

Our research study results revealed that hypertension and atrial fibrillation (AF) were common in the Parkinson disease group with statistically significant differences between the groups (p value <0.001, 0.012) respectively, while there were no significant differences between the examined groups concerning DM (p value = 0.729).

Our results revealed no statistically significant difference between patients and controls in terms of studied laboratory data (ALT, AST, HbA1C, CHOL, TG, LDL, HDL, ESR, and CRP) (p-value > 0.05).

Lubomski et al. [15] found that patients with PD had lower total cholesterol levels (4.8; SD 0.9 versus 5.2; SD 1.1, p = 0.014), lower HDL levels (1.4; SD 0.4 versus 1.6; SD 0.4, p = 0.033), and lower albumin levels (38.7; SD 3.5 versus 39.8; SD 3.1, p = 0.023). As regards ESR, C-RP, Low-Density Lipoprotein, triglycerides, and random glucose level, there have been no statistically significant differences between the two groups.

Our results revealed that gastrointestinal tract symptoms preceded the motor manifestations of PD disease and there were highly statistically significant differences between Parkinson's disease and Healthy Control concerning the Cleveland Constipation Score (CCS) and the Leeds Dyspepsia Questionnaire (LDQ) Score (p-value < 0.001).

Lubomski et al. [15] showed that 78.6% of PD patients had definitive functional constipation, as defined using the Rome-IV criteria (score 2, range 0–15), compared to 28.4% of healthy controls (p 0.001). Constipation was more common in PD patients, with a mean score of 4.4 (SD 3.5) versus 1.1 (SD 1.4) (p 0.001) and an odds ratio of 9.3 (95% CI 4.7–18.2). Furthermore, the CCS (range 0–30) revealed that PD patients had more severe constipation: 7.2 (SD 4.7) versus 3.1 (SD 2.9) in HCs (p 0.001), which matched our findings.

According to Lubomski et al. [15,] in the PD cohort, upper GI dysfunction as measured on the LDQ (range 0–40) was associated with greater severity of symptoms, with participants indicating more indigestion (18.4 % versus 8.6 %), nausea (15.6 % versus 7.4 %), and excessive fullness and bloating (20.4 % versus 14.8 %) (p = 0.034). Furthermore, the PD group's mean LDQ score (8.3; SD 7.7) was greater (p = 0.001) than the HC group's (4.6; SD 6.1), indicating a higher severity of symptoms, which is consistent with our findings.

Skjærbæk et al. [18] in a review that provided a brief summary of GI pathophysiology in PD and highlighted particular GI symptoms and objective measurements of dysfunction that are essential for future study, revealed that subjective GI symptoms are widespread in PD and the incidence of objectively assessed dysfunction is much greater.

Cersosimo et al. [17] discovered that PD patients had considerably greater dry mouth, dysphagia, drooling, constipation, as well as defecatory dysfunction than controls, and that all PD patients confirmed at least one GIS, compared to 67.5% (81 of 120) controls (p = 0.001). In the PD group, the median number of GIS per person was 5 (3–6), compared to 1 (0–2) in the controls (p = 0.001).

This study's strengths include its prospective study design and the fact that no patients were lost to follow-up during the study. This study defines the occurrence of gastrointestinal tract symptoms in PD with a correlation to the existence or lack of gastrointestinal tract symptoms with the stages of the disease.

Specific shortcomings are worth mentioning in this study, including the study's smaller sample size compared to other studies, the fact that it was not a multicentric study, Cersosimo et al. [17] featured a total of 249 patients and the possibility of publication bias. Another disadvantage is the dependence on the patient's memory as the sole source of information for evaluation. On the other hand, our findings are comparable with those of large studies that used standardized questionnaires.

CONCLUSION

Our results point to new clinical relationships and their implications for GI dysfunction in Parkinson's disease. The most common gastrointestinal premotor symptoms of PD were constipation and defecatory dysfunction.

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