The Relation of Gastrointestinal Symptoms to Duration of Levo-dopa Treatment and Severity of Parkinson's Disease

Aynur Özge, MD*
Resul Bugdayci, MD*
Eedem Toğrol, MD†
Mehmet Saraçoglu, MD†

*Mersin University School of Medicine, Mersin, TURKEY
† GATA Haydarpasa Training Hospital, Istanbul, TURKEY

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KEY WORDS: Parkinson's disease, gastrointestinal symptoms, response to levo-dopa, duration of treatment, severity of disease, Hoehn & Yahr Scale

ABSTRACT

This study was undertaken to determine the frequency of gastrointestinal (GI) symptoms (abnormal salivation, dysphagia, heartburn, nausea, vomiting, loss of appetite, abdominal bloating-distension, and constipation), and to evaluate its relation with both the severity of Parkinson's disease and the duration of the levo-dopa treatment. Sixty-three Parkinson's disease (PD) patients and 21 healthy age-matched controls were included in this study. Forty-eight patients (76.1%) with PD and 4 controls (19.0%) reported GI symptoms ($P = 0.003$). Most common symptoms were loss of appetite and abdominal distension (71.4%) in patients and loss of appetite in controls, and there is a significant correlation between the duration of treatment and the number of GI symptoms ($r = 0.261$; $P = 0.03$). It was concluded that close monitoring of GI symptoms in all stages of PD might help to evaluate response to levo-dopa, especially in line with longer duration of disease and treatment.

INTRODUCTION

Parkinson's disease (PD) remains one of the most common neurodegenerative diseases, affecting 1% of the population over age 65.[1] Autonomic disorders are often seen in idiopathic Parkinson's disease, especially in the advanced stage of PD. The symptoms may include gastrointestinal, sudomotor, thermoregulatory, and bladder abnormalities[2] as well as cardiovascular symptoms, such as abnormal blood pressure responses (orthostatic hypotension and abnormal circadian blood pressure rhythm).[3] Disturbances of the gastrointestinal (GI) tract are considered to be the most frequent autonomic disorders in PD.[4,5] Common symptoms of GI dysfunction include abnormal salivation, difficulty on swallowing (dysphagia), early feeling of satiety (abdominal bloating-distension), disorders of gastric emptying, and constipation. While the pathophysiology of these symptoms is unclear, they have attributed to the cerebral degeneration and accumulation of Lewy

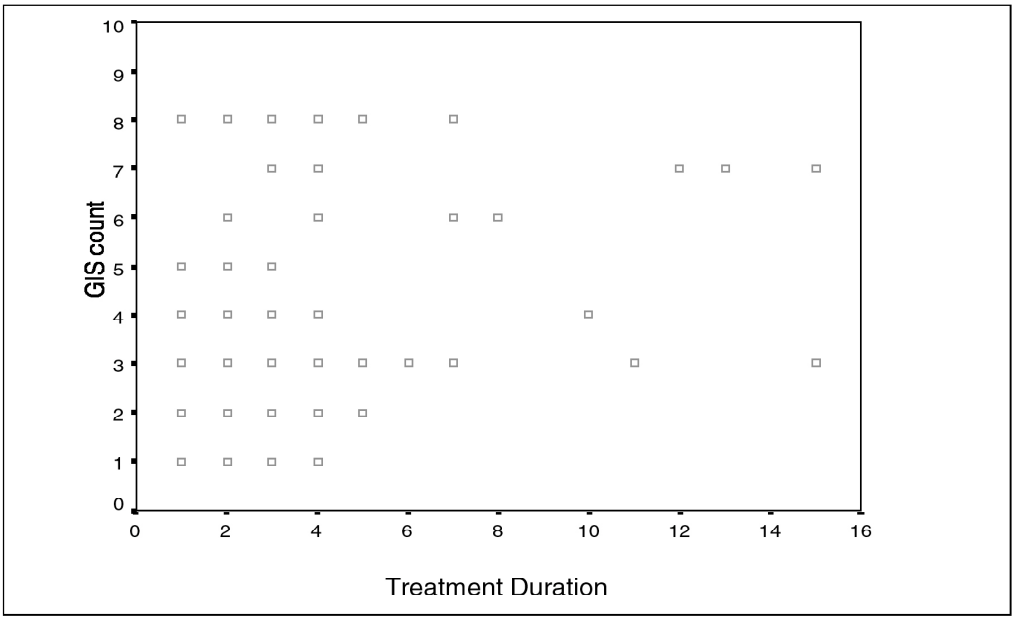

Figure 1. Scattergam showing significant correlation between the duration of treatment (year) and the number of gastrointestinal symptoms ($r = 0.261$, $P = 0.03$) in Parkinson's disease patients.

bodies in the myenteric and submucosal plexus within the gastrointestinal tract.[6-10]

Abnormal salivation is one of the classical symptoms in the early stages of parkinsonism. Recent studies have revealed that abnormal salivation is not due to an increase of saliva production but results from the accumulation of saliva relating to dysphagia.[6,11] The first symptom of disturbed saliva production is the dribbling of saliva on the bed while asleep, which occurs in up to 86% of the patients.[11]

While PD may affect all stages of swallowing, the most pronounced effects are the oropharyngeal and esophageal stages. Dysphagia is compounded by loss of power and rigidity in masticator musculature.[6,11-13] If a burning pain accompanies the dysphagia (heartburn), this is probably due to gastroesophageal reflux[11]. Dysphagia develops in approximately 50% of patients and may be a reflection of both central nervous system and enteric nervous system derangement.[14] Choking and coughing are complaints in 30% of these patients.[1]

Nausea, vomiting, and anorexia (loss of appetite) are symptoms that may be attributed to gastric motility. Gastric emptying may be delayed due to decreased parasympathetic activity.[6,7,11,15,16] Evans et al[17] reported that the gastric emptying is disturbed in approximately 55% of the patients with PD. Levo-dopa may also delay gastric emptying, causing a vicious cycle that impairs compliance with therapy.[6,16,18]

Bowel dysfunction in PD may be result of both delayed colon transit and impaired anorectal muscle coordination.[14] Abdominal bloating and distension, formerly attributed to motor dysfunction of the small intestine,[11] are currently considered to be a colonic syndrome.[19] Constipation has been reported in over 50% of patients with PD attending a clinic.[6,7,11] Constipation may result from several factors, including impaired relaxation of pelvic floor muscles driving defecation.[6,7,11] In addition, colonic and anorectal dysfunction appears to be an early GI manifestation of PD, and may represent the direct involvement of the gut by this process.[19] The medications used to treat PD without exception all have the potential to exacerbate constipation.[1]

This clinically based cross-sectional study was undertaken to determine the fre-

Table 1. Demographic and clinical data of patients and controls.

Characteristics	Patients (n = 63)	Controls (n = 21)
Sex (M/F)	31 (49.3%) / 32 (50.7%)	9 (42.9%) / 12 (57.1%)
Mean age (year)	65.4 ± 10.1	62.3 ± 7.3
Family history of movement disorders	25 (39.6%)	None
Number of smoking subjects	21 (33.3 %)	3 (14.2%)
Disease duration (years)	6.1 ± 5.3 (ranges 1-25)	-
Treatment duration (years)	4.1 ± 3.4 (ranges 1-15).	-
The presenting symptom;		-
Tremor	51 patients (80.9%)	
Bradykinesia	9 patients (14.3%)	
Postural abnormality	3 patients (4.8%)	
One-sided presentation of symptoms	46 patients (73%)	-
Mean H&Y score	2.1 ± 1.0	-
Mean UPDRS	35.6 ± 20.9	-
Mean S&E ADL score (%)	70.6 ± 18.7	-

Key: H&Y: Hoehn & Yahr Score; UPDRS, S&E ADL

quency of gastrointestinal (GI) symptoms, and to evaluate the relation of these symptoms (abnormal salivation, dysphagia, heartburn, nausea, vomiting, loss of appetite, abdominal bloating-distension, and constipation), to both the severity of Parkinson's disease and the duration of levo-dopa treatment.

METHOD

Sixty-three patients were included in the study. These subjects were being followed up in our PD and Movement Disorders Outpatient Department and were diagnosed as having PD according to the strict criteria of Bower et al.[20] The control group consisted of 21 healthy age-matched subjects (see Table 1). Subjects with a history of neuromuscular disease, peptic ulcer, or gastrointestinal surgery were excluded from this study. Informed consent was obtained from each of the subjects.

We recorded the demographic and clinical features of each subject via a structured interview by the same neurologist. The severity of PD was evaluated by United Parkinson's Disease Rating Scale (UPDRS), Modified Hoehn and Yahr (H&Y) Scale, and Schwab and England Activities of Daily Living Scale (S&E ADL).[21] The patients were divided into 2 groups according to the H&Y scale: those below the second stage (mild/moderate disease) and those above (advanced PD).

Gastrointestinal symptoms (i.e abnormal salivation, dysphagia, burning pain in the chest, nausea, vomiting, loss of appetite, abdominal distension, and constipation) were assessed and rated according to severity (1, mild; 2, medium; 3, severe), as defined by Edwards et al[11] and Jost [6] previously.

Because our patient samples with H&Y stages I and V were small, patients with mild/moderate (early stage, stage 1, and stage 2, n = 41) or more severe PD (advanced levels over stage 2, n = 22) were grouped together for exploratory statistical purposes. χ^2 was used to test hypotheses about categorical variables. The relation of gastrointestinal symptoms of the patient group to the severity of symptoms and the duration of levo-dopa treatment (5 years or less, 6 years or more) was evaluated by logistic regression analysis and Pearson correlation analysis. In logistic regression

Table 2: Comparison of study groups according to presence of gastrointestinal symptoms.

Symptoms	Patients n = 48 (%)	Controls n = 4 (%)	*P*	χ^2	OR	95% CI Lower - Upper
Abnormal salivation	43 (68.3%)	1 (4.8%)	0.000	25.45	0.23	0.003 - 0.186
Dysphagia	19 (30.2%)	2 (9.5%)	0.050	3.57	0.24	0.052 – 1.152
Heartburn	19 (30.2%)	0	0.002	8.18	0.69	0.594 – 0.821
Nausea	34 (54.0%)	2 (9.5%)	0.000	12.70	0.09	0.019 – 0.418
Vomiting	16 (25.4%)	0	0.009	6.58	0.74	0.646 – 0.862
Loss of appetite	45 (71.4%)	4 (19.0%)	0.000	17.78	0.09	0 028 – 0.318
Abdominal distension	45 (71.4%)	2 (9.5%)	0.000	24.49	0.04	0 009 – 0.200
Constipation	37 (58.7%)	3 (14.3%)	0.000	12.47	0.11	0 031 – 0.439

OR: Odds ratio

* Number of subjects

analysis, any GI symptoms and duration of levo-dopa treatment were accepted as the dependant variables. The following variables were tested in this model: age, sex, family history, presenting symptoms, disease duration, duration of treatment, presence of additional systemic diseases, use of tobacco, severity of disease, UPDRS, and S&E ADL scores. The means were calculated with descriptive statistics. Two-tailed tests were used in this study. The tests were considered significant at the 5% level.

RESULTS

Forty-eight PD patients (76.1%) and 4 controls (19%) had at least 1 type of GI dysfunction symptom ($P = 0.003$). The demographic and clinical features both of the patients and controls are summarized in Table 1.

Most of the patients (42.8%) were women who did not work outside the home. An additional medical problem (i.e., chronic obstructive pulmonary disease, non-insulin dependent diabetes mellitus, and glaucoma) was reported in 24 subjects (38.1%).

Most common symptoms were loss of appetite and abdominal distension (71.4%) in patients and loss of appetite (19.0%) in controls. All of the GI symptoms were significantly higher and severe in patients than in controls (see Table 2). Also, vomiting and heartburn were the most common symptoms in patients with PD (OR, 0.74 and 0.69, respectively).

Most of the patients with PD had a mild or moderate H&Y score (early PD; 41 patients, 65%). As seen in Table 3, except for nausea, all of the GI symptoms occurred at a statistically higher rate in patients with advanced PD than early PD. In this group, the most common symptoms were constipation and abdominal distension (OR, 7.43 and 6.28, respectively).

When a comparison was made according to duration of levo-dopa therapy (Table 4), dysphagia (χ^2 4.36; df,1; $P = 0.03$) and loss of appetite (χ^2 6.55; df,1; $P = 0.007$) were more prevalent with longer duration of treatment.

Patients with GI symptoms showed significantly increased H&Y Scores [OR, 2.65, 95% CI for OR, 1.24-5.65; $P = 0.01$]. In addition, patients with longer levo-dopa treatment duration had significantly higher H&Y Scores [Exp(B): 6.40; 95% CI for Exp(B): 1,68-24,37; $P = 0.0000$]. As shown in Figure 1, there is a significant correlation between the duration of levo-dopa treatment and the number of GI symptoms ($r = 0.261$; $P = 0.03$).

Table 3: Comparison of gastrointestinal symptoms according to disease severity.

Symptoms	Early PD (n = 41)	Advanced PD (n = 22)	*P*	χ^2	OR	Lower - Upper 95% CI
Abnormal salivation	24 (58.5%)	19 (86.4%)	0.02	5.11	4.48	1.14-17.60
Dysphagia	9 (22.0%)	10 (45.5%)	0.05	3.75	2.96	0.96-9.06
Heartburn	9 (22.0%)	10 (45.5%)	0.05	3.75	2.96	0.96-9.06
Nausea	21 (51.2%)	13 (59.1%)	NS	0.35	1.37	0.48-3.92
Vomiting	7 (17.1%)	9 (40.9%)	0.03	4.29	3.36	1.03-10.90
Loss of appetite	26 (63.4%)	19 (86.4%)	0.05	3.69	3.65	0.92-14.43
Abdominal distension	25 (61.0%)	20 (90.9%)	0.01	6.28	6.40	1.31-31.10
Constipation	19 (46.3%)	18 (81.8%)	0.006	7.43	5.21	1.50-18.10

NS: Difference not statistically significant ; OR: Odds ratio;
CI: Confidence interval

DISCUSSION

Patients with PD may have autonomic dysfunction. In fact, PD is categorized as a disease of unknown cause that involves primary autonomic failure.[22,23] Forty-eight patients with PD (76.1%) and 4 control subjects (19%) reported GI symptoms in this study. GI symptom frequency in our patients was similar to previous reports.[6,11]

The frequency of abnormal salivation has been reported ranging from 70% to 78%,[8,12] whereas, this rate ranges from 6% to 12% in matched healthy individuals. The frequency of abnormal salivation is 68.3% in patients with PD, although none of the controls in this study were similar to those in other studies. Likewise, the severity of abnormal salivation was found to be remarkably higher in the PD group ($P = 0.000$). Abnormal salivation was seen in both new patients and patients with advanced PD, and no relation could be shown with the duration of L-dopa use. Other studies[11,12] have reported a direct relation between the severity of the disease and the salivation disorder. In the patient group of the present study, no significant difference could be shown for the frequency of abnormal salivation between the early PD patients and advanced PD patients.

Dysphagia has often been reported in PD patients, especially in more advanced disease levels. This problem has been reported to be between 50% and 95% in most studies.[6,11,12] In Leopold et al[13] the researchers evaluated the swallowing function of 71 idiopathic PD patients complaining of dysphagia. With dynamic videofluoroscopy it was shown that dysphagia is not a finding seen in early PD. The researchers also reported that as the disease process evolves, various lingual, pharyngeal, and esophageal degenerative changes are seen that are related to this problem. Bushman et al[24] have reported that disease severity is not a determining factor for the occurrence of dysphagia in PD. While levo-dopa treatment regresses the cardinal findings of PD, it also partially reduces the dysphagia. Levo-dopa treatment is reported to cause a 40% improvement in pharyngeal function. Dysphagia frequencies of 30.2% for the patient group and 9.5% for the controls in the present study are remarkably lower than the frequencies reported in the literature. This can be explained by the fact that the majority of our patients (65.0%) are in the early phases of PD and levo-dopa therapy (mean 4.1 ± 3.4 years).

It has been reported that a burning pain in the chest is usually related to gastroesophageal reflux in PD and that it is seen in approximately 26% of patients.[11,13] The fre-

Table 4: Comparison of frequency of gastrointestinal symptoms between treatment groups.

Treatment duration Symptoms	< 5 years (n = 50)	5 years (n = 13)	*P*	χ^2	OR	95% CI Lower - Upper
Abnormal salivation	33 (66.0%)	10 (76.9%)	NS	0.56	1.71	0.41-7.08
Dysphagia	12 (24.0%)	7 (53.8%)	0.03	4.36	3.69	1.04-13.14
Heartburn	13 (26.0%)	6 (46.1%)	NS	1.99	2.44	0.69-8.60
Nausea	27 (54.0%)	7 (53.8%)	NS	0.0	0.99	0.29-3.38
Vomiting	12 (24.0%)	4 (30.7%)	NS	0.25	1.40	0.36-5.40
Loss of appetite	32 (64.0%)	13 (100%)	0.007*	6.55	1.40	1.16-1.69
Abdominal distension	33 (66.0%)	12 (92.3%)	NS*	3.49	6.18	0.74-51.61
Constipation	29 (58.0%)	8 (61.5%)	NS	0.53	1.15	0.33-4.04

NS: Difference not statistically significant; OR: Odds ratio;
CI: Confidence interval* Fisher Exact Test

quency of these symptoms in the patient group (30.2%) is significantly higher than the control group. Additionally, the frequency of this symptom was found to be unrelated to disease level and duration of levo-dopa therapy.

In the study of Soykan et al[7], in which gastric myoelectric activity was evaluated with electrogastrography (EGG), it was concluded that the gastrointestinal tract was affected in the primary disease process. The frequency of the disturbance of gastric emptying caused by this involvement has been reported to be 55% by Evans et al.[17] The disturbance of gastric emptying causes symptoms like postprandial sense of fullness, nausea, loss of appetite, early feeling of satiety, and vomiting.[6,11,18] Levo-dopa therapy increases these symptoms.[16,24] Among the patients of the present study, all of whom use levo-dopa, the frequency of reported nausea was 54%, vomiting 25.4%, and loss of appetite 71.4%, while the ratios for the control group were 9.5% (frequency of reported nausea) , 1% (vomiting), and 19% (loss of appetite). The severity of symptoms other than loss of appetite did not differ significantly between the 2 groups. Yet, it was determined that while disease level does not affect nausea and loss of appetite, vomiting was more frequent among patients with more advanced disease. A long duration of levo-dopa use might be related to the loss of appetite by Djaldetti et al[16] confirmed that because the plasma levo-dopa levels increase and decrease quickly due to the gastric emptying disturbances, there is an increase in motor fluctuations. Five subjects (7.9%) in our patient group showed motor fluctuations (on-off phenomena) during levo-dopa treatment. But since we could not make electrogastroscopic investigations, we cannot determine the frequency of gastric emptying defect and its effect on the motor fluctuations.

Constipation is the most frequent autonomic disturbance seen in PD patients with a frequency reported to be between 50% and 74% (10% to 28% in healthy controls).[7,11,12] The frequency of abdominal distension was 71.4%, and constipation was 58.7% in the patient group, while the frequencies in the controls were 9.5% and 14.3%, respectively. These ratios are similar to those in the relevant literature. The severity of symptoms did not differ in the patient and control groups. Yet, both symptoms were seen more frequently in patients with an advanced level of disease. No relation was found with the duration of levo-dopa treatment.

This study has 2 limitations. First, we did not use a standardized bowel diseases questionnaire, although we used a structured interview by the same neurologist. Second,

this study is a clinical study, not in a population-based study. For this reason our results cannot be generalized.

We have shown that abnormal salivation, heartburn, dysphagia, nausea, and loss of appetite were more frequent in early PD, and vomiting, abdominal distension and constipation in advanced PD. In addition, dysphagia and loss of appetite were associated with a longer duration of levo-dopa treatment. It was concluded that close monitoring of gastrointestinal symptoms in all stages of PD might help to evaluate response to levo-dopa, especially in line with longer duration of treatment.

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