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Leslie J. Cloud, MD Date

Gastrointestinal Symptoms in Parkinson's Disease: Prevalence, Characterization, and Relationship to Disease Stage

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Gastrointestinal Symptoms in Parkinson's Disease: Prevalence, Characterization, and Relationship to Disease Stage

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MD, Medical College of Georgia, 2004

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An abstract of a thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Master of Science in Clinical Research

2011

Abstract

Gastrointestinal Symptoms in Parkinson's Disease: Prevalence, Characterization, and Relationship to Disease Stage

By Leslie J. Cloud

Despite their high prevalence and well-documented impact on quality of life, the gastrointestinal (GI) features of Parkinson's Disease (PD) remain scarcely investigated, poorly understood and without effective treatments. Though once thought to be a late manifestation of the disease, emerging pathological data has implicated the enteric nervous system (ENS) as one of the earliest anatomic sites to manifest Parkinson's disease histopathology, and recent clinical data has suggested that GI symptoms such as constipation can manifest very early in the disease course, sometimes occurring years prior to the onset of motor features. These findings have led to the controversial hypothesis that the PD pathological process begins in the ENS and subsequently spreads to involve the central nervous system, at which time the classic motor features develop. Very few studies have explored the relationship between GI and motor symptoms in PD. Therefore, this study was designed to help clarify this relationship as well as to estimate the prevalence of GI symptoms in PD and better characterize them. To accomplish these aims, a novel scale for quantifying GI symptoms in PD was designed and piloted in 61 PD patients and their spousal controls. Results not only confirm that the prevalence and severity of GI symptoms are higher in PD than controls, but also that the prevalence and severity of GI symptoms in PD increase as the motor features of the disease advance. Results also suggest that PD patients respond poorly to symptomatic GI medications, underscoring the need for novel therapeutic approaches.

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Introduction

Parkinson's disease is a common neurodegenerative disease often presenting with the well-recognized triad of motor symptoms comprised of tremor, rigidity (stiffness), and bradykinesia (slowness of movement). The severity of the aforementioned motor symptoms is traditionally staged according to the Hoehn and Yahr (H&Y) scale, which is featured in Appendix 1 (1). In addition to the motor symptoms of the disease, PD patients can have a variety of non-motor symptoms (NMS), of which GI symptoms are among the most common (2). The spectrum of GI symptoms in PD is diverse and can include sialorrhea (drooling), dysphagia (trouble swallowing), early satiety (feeling full), nausea and vomiting from delayed gastric emptying, bloating from poor small bowel coordination, constipation from slow colonic transit, defecatory dysfunction, and weight loss (2).

GI symptoms have many important ramifications for PD patients. Multiple recent studies have underscored the importance of GI symptoms in determining quality of life in PD (3-5). Furthermore, GI symptoms can be associated with serious and potentially life-threatening complications such as malnutrition, pulmonary aspiration, megacolon, intestinal pseudo-obstruction and even perforation, and they rank among the most common causes for emergency admission in the PD population (2, 6). GI symptoms can also affect other PD symptoms. For example, delayed gastric emptying can lead to erratic absorption of oral PD medications, thereby contributing to increased motor fluctuations and medication side effects (7-10). Despite their significance for PD patients, GI symptoms remain scarcely investigated, poorly understood, and without effective treatments.

The relationship of the GI and motor features of PD is currently under revision. Though once thought to be a relatively late manifestation of the disease, emerging pathological data has implicated the ENS as one of the earliest anatomic sites to manifest Parkinson's disease histopathology, and recent clinical data suggested that GI symptoms such as constipation can occur very early in the course of PD, sometimes occurring years prior to the onset of the classic motor features of the disease (11, 12). These findings have led to the controversial hypothesis that the PD pathological process begins in the ENS and subsequently spreads to involve the central nervous system, at which time the classic motor features develop.

The study presented herein was undertaken with the goals of evaluating the severity and prevalence of GI symptoms in PD, better characterizing GI symptoms (including response to commonly used symptomatic GI medications), and clarifying the relationship between GI and motor symptoms. In order to accomplish these aims, a novel scale for quantifying GI symptoms in patients with PD (the Gastrointestinal Symptoms in Neurodegenerative Disease scale or GIND) was designed and piloted in 61 PD patients and their spousal controls.

Background

There is a paucity of prevalence data on GI dysfunction in PD, and existing estimates vary widely, likely as a result of methodological differences across studies (13-15). To our knowledge, no prior studies have reported prevalence data for GI symptoms across the H&Y stages of PD. More work is thus needed to establish accurate prevalence data on GI symptoms in PD and to clarify how prevalence may relate to H&Y stage.

Only one other group has previously looked at the relationship between GI symptom severity and H&Y stage. Using a survey of PD patients, these investigators reported a roughly linear correlation between the severity of some GI symptoms and H&Y stage (13). This was interpreted as evidence supporting the hypothesis that GI symptoms are caused by a direct effect of the PD pathological process acting on the ENS. However, very few patients with very early PD (H&Y stage 1) were included in that study. Since other features of an advancing neurodegenerative disease (increased age, medication administration, etc…) can influence GI symptoms, a determination as to whether GI symptoms correlate with H&Y stage in *early* disease would provide more compelling data to support this hypothesis. Furthermore, rigorously controlling for all of these potential confounders in the analysis would strengthen these conclusions.

With this background in mind, this study was designed to evaluate the severity and prevalence GI symptoms, with particular emphasis on the relationship between the GI and motor symptom manifestation, in a sample enriched with early PD patients (H&Y stages 1 and 2). Data on appropriate confounding variables was collected and these variables were controlled for in the analysis.

Methods

Null Hypotheses and Specific Aims

Aim 1. To quantify the severity of GI symptoms in a sample of PD patients, as measured by the GIND total score, and compare it to that in a sample of non-Parkinsonian controls.

Null hypothesis: The severity of GI symptoms in the PD group is statistically equal to that in the control group.

Subaim. To estimate the prevalence of GI symptoms in the PD population.

Aim 2. To fully characterize the GI dysfunction occurring in a sample of PD patients.

Aim 3. To determine if GI symptom severity, as measured by the GIND total score, is associated with H&Y stage when controlling for appropriate confounding variables.

Null hypothesis: There is no association between GI symptom severity and H&Y stage after controlling for appropriate confounding variables.

Study Design

This was a cross-sectional study. The GIND was administered via telephone by a single interviewer (Dr. Leslie Cloud) to a sample of PD patients and their spouses at a single point in time. Our use of spouses as controls was intended to control potential confounding of age, diet, and other unmeasured environmental and social factors. There is a precedent of using spousal controls in studies of GI symptoms for this reason (13). Phone interview was chosen to ensure complete and accurate data collection in a convenient manner. Patients and their spouses were interviewed separately.

Characteristics of the Population

A convenience sample was recruited in the movement disorders clinic at Wesley Woods Health Center, at PD support group meetings, and by telephone between October of 2007 and August of 2010. To be considered for inclusion, subjects were required to have a known diagnosis of PD, managed medically rather than surgically, and a spouse who was also willing to participate. Couples were excluded on the basis of cognitive dysfunction in either the PD patient or their spouse that might interfere with the collection of accurate data. Couples were also excluded on the basis of GI disturbance from other known causes in either the PD patient or their spouse. Figure 1 summarizes subject screening and enrollment.

Table 1 summarizes the baseline characteristics of the study population. The mean age of this PD sample accurately reflected the underlying PD population, in which the average age of onset is 62 years (16). The gender distribution in this sample also accurately reflected the underlying population since PD is more common in men (16). Because we do not attract a racially heterogeneous population at our center, our PD sample did not accurately reflect the racial diversity of the underlying PD population. The distribution of H&Y stage in this sample was heavily weighted toward early stages of disease (stages 1 and 2), though subjects with more advanced stages of disease (stages 3 and 4) were also included. No stage 5 patients were available for screening during the enrollment period. PD patients may manifest varying amounts of the cardinal motor features and are thus sub-categorized as having one of 3 motor phenotypes: akinetic-rigid patients who manifest mainly rigidity and bradykinesia, tremor-predominant patients who manifest predominantly tremor, and mixed patients who have roughly equal amounts of

all three cardinal motor symptoms. The distribution of motor phenotype in this sample was characteristic of the underlying population, in which the mixed phenotype is the most common form (17).

Regarding relevant PD medication usage, 75% of the PD subjects were taking dopaminergic medications (levodopa or dopamine agonists) for their motor symptoms, and 28% were taking anticholinergic medications for either motor symptoms or overactive bladder.

Outcome Variable

In order to accomplish the aims of this study, a method for quantifying GI symptoms in PD was needed. A questionnaire or rating scale was felt to be the most appropriate option given the broad spectrum of GI symptoms that occur in PD and given that clinical tests that directly measure GI function are invasive, expensive, and can pose significant risk to study subjects. Very few pre-existing scales quantify GI symptoms in PD. There are symptom-specific scales that focus on individual GI symptoms in PD (18, 19). Global scales exist for the quantification of autonomic symptoms and non-motor symptoms in PD; however, these scales do not cover the full range of GI symptoms that can occur in PD (20, 21). Only one comprehensive GI symptom scale was previously designed for PD population, but it was never adopted by other groups and was never published in full form (13). Thus, it was determined that a new scale was needed that would cover all of the GI symptoms known to occur in PD but that could be still administered quickly.

With the help of collaborators in the division of digestive diseases at Emory, a novel scale for the quantification of GI symptoms in PD (the GIND) was designed. The GIND covers the 12 GI symptoms that are known to occur in association with PD, along with a question about how the GI symptoms affect quality of life. As a Likert-type scale, the GIND asks patients to rate each of their GI symptoms on a 0-5 scale with higher scores representing more severe GI dysfunction. The maximum score one can achieve is 65. The GIND only covers the 2 weeks prior to survey to avoid significant recall bias.

Because this novel tool had not been previously assessed, there was uncertainty about its validity, reliability, and internal consistency. However, using the pilot data from this study, subsequent analyses were performed to assess the validity and reliability of the GIND and are discussed herein.

Because the GIND was designed to cover all of the GI symptoms known to occur in association with PD, as determined by a comprehensive review of the literature, it was felt to have inherent content validity. Exploratory factor analysis was performed on the pilot dataset to evaluate patterns of associations between the items on the scale, and the results support the construct validity of the GIND, as the 3 resulting factors correspond to biologically meaningful constructs. Details of the factor analysis methods, results, and interpretation are presented in Appendix 2. Regarding criterion validity, the GIND performed the task for which it was designed, differentiating PD patients from controls and even differentiating the various H&Y stages represented in our PD sample. Furthermore, the results of this study are consistent with previously published results from other groups and therefore support the criterion validity of the GIND. Regarding reliability and internal consistency check, the overall Cronbach coefficient alpha for the

GIND using the pilot dataset was found to be 0.802, which falls within the acceptable range for research purposes. In an effort to screen for problematic questions that may have brought the overall alpha down, each variable was individually deleted, and the overall alpha recalculated with the variable deleted. Results of this analysis confirm that the overall alpha was not substantially improved by the deletion of any individual variable.

Predictor Variables

The severity of motor symptoms is most commonly staged according to the H&Y staging system, which is presented in Appendix 1. H&Y stage was thus selected as the primary independent variable of interest. Several other independent variables were considered for inclusion in the model, including the following potential confounders: age, sex, dopaminergic medication use, and anticholinergic medication use. Both anticholinergic and dopaminergic medications can cause GI side effects, and are thus important variables to control for in a study of GI symptoms in PD. Similarly, age and gender may influence GI symptom expression and are thus important variables to control for in a study of GI dysfunction. Patients with PD can have variable amounts of each of the cardinal motor symptoms and are thus subcategorized as having one of 3 motor phenotypes: akinetic-rigid, tremor-predominant, and mixed patients. Motor phenotype was also considered for inclusion in the model as a potential effect modifier, as it is biologically plausible that the relationship between H&Y stage and GI symptoms severity differs between the motor phenotypes, which can differ considerably in their levels of overall mobility and activity.

Variable Measurement

Electronic medical records were used to determine the motor phenotype of all PD subjects according to previously-published criteria (17). Electronic medical records and information obtained via telephone interview were used to determine the H&Y stage of all PD subjects. Data on age, gender, race, and relevant medication usage was obtained verbally from subjects at the time of GIND administration.

Sample Size

At study inception, nothing was known about the variability of the study's primary outcome measure because the GIND had not been previously piloted. The pilot data from this study will be used to determine sample size in future studies using the GIND.

Analysis

Because the distribution of GIND scores was non-normal, the GIND scores were transformed using the Ln GIND total score, which has a more normal distribution. Appendix 3 features a comparison of the two distributions. Ln GIND was subsequently used for the portions of the analysis that were based upon the assumption of normality, and the untransformed outcome was used where possible.

For Aim 1, the GIND total scores for PD and controls were compared using a Wilcoxon rank sum test. To test the effect of H&Y stage and group (PD vs. control) on Ln GIND, and also to assess for interaction between stage and group, a subgroup analysis was subsequently performed using 2-way ANOVA and Bonferroni post-tests. In order to

determine the sample prevalence of GI symptoms in PD, a cut point in the GIND total score (above which one was considered to have an abnormal amount of GI symptoms) was selected. Using clinical judgment, a score of 10 was felt to be the highest score one could have and still be considered within normal limits. Analysis of the GIND quantiles for control patients revealed that a GIND score of 10 corresponded to the 95^{th} percentile. Ten was thus selected as the most appropriate cut point to use in the sample prevalence calculations on both clinical and statistical grounds. Sample prevalence was calculated using this cut point of 10 and was subsequently used to estimate the population prevalence. An approximate 95% confidence interval for the for the population prevalence was calculated using the following formula for large samples (criteria for "large" sample met because np and n(1-p) were both ≥ 5), where p=sample prevalence and n=number of subjects:

$$p \pm Z_{\alpha/2} \sqrt{(p(1-p)/n)}$$

For aim 2, the proportions of PD and control subjects having individual GI symptoms and utilizing various symptomatic GI medications were compared using chi-squared tests and Fisher exact tests where appropriate. Controls were left out of the analysis for aim 3, which involved a multiple linear regression using Ln total GIND score as the outcome variable and H&Y stage as the primary independent variable of interest. Design variables were created where appropriate. Several other independent variables were initially included in the model, including the following potential confounders: age, sex, dopaminergic medication use, and anticholinergic medication use. Motor phenotype was included in the initial model as a potential effect modifier. Variables were deleted

individually, and the resulting models were re-analyzed in order to determine the best final model.

Results

Aim 1

The median GIND total score was significantly higher in PD than in controls (Figure 2), and it increased with H&Y stage (Figure 3). Subgroup analysis comparing individual H&Y stages with their matched controls revealed that GIND total score was significantly higher in PD than controls for all H&Y stages (Figure 4 and Table 2). Two-way ANOVA also revealed no significant stage-group interaction (Table 2).

The prevalence of GI symptoms in the PD sample was 44% versus 5% among controls, resulting in a sample prevalence ratio of 8.8. The approximate 95% confidence interval for the PD population prevalence was found to be 32 to 57 percent. Figure 5 features the prevalence of GI symptoms by H&Y stage.

Aim 2

Statistical evaluation of the frequency of individual GI symptoms in PD versus controls is summarized in Table 3. The prevalence of all of the GI symptoms was higher in PD than in controls, though this difference was not statistically significant for all symptoms. Dysphagia, sialorrhea, early satiety, constipation, defecatory dysfunction, and weight loss were all significantly more prevalent in PD than in controls, while nausea, vomiting, anorexia, bloating, abdominal pain, and excessive gas were not significantly more prevalent in PD. Table 4 features the prevalence of individual GI symptoms by H&Y stage. Different GI symptoms correlated differently with PD stage. For example, upper GI symptoms such as sialorrhea and dysphagia were uncommon in stages 1 and 2, but became highly prevalent in stages 3 and 4. Conversely, some lower GI symptoms

such as defecatory dysfunction were present in nearly half of stage 1 patients, and the prevalence continued to increase in later stages of disease.

Data on medication usage found that PD patients used symptomatic GI medications (predominantly for constipation) at high rates that increased as the disease advanced (Figure 6). Thirty-eight percent of PD patients versus only 8% of controls took at least 1 daily medication for constipation ($p=0.0002$). Table 5 features the types of laxatives used by patients and controls. Of those taking daily medications for their GI symptoms, 20% of PD patients versus only 3% of controls reported a poor response to these medications ($p=0.0317$).

Aim 3

Table 6 presents the final model selected, and table 7 features the ANOVA table for the final model. As shown in table 6, even after controlling for age, sex, and dopaminergic medication use, GI symptom severity is still associated with H&Y stage.

Discussion

Results confirm that PD patients experience significantly more GI symptoms than healthy controls at all H&Y stages, and the severity of GI dysfunction increases as the motor features of disease advance. The interaction term in the 2-way ANOVA, which was intended to explore the potential significance of unmeasured variables within couples (e.g. dietary factors) and their influence on GIND scores, suggests that these unmeasured variables are not significant. The prevalence estimate of 44% falls within the range of previously reported prevalence estimates for GI dysfunction, which vary widely, and to our knowledge this is the first study to report data on the prevalence of individual GI symptoms by H&Y stage.

Prior studies have shown weight loss, sialorrhea, dysphagia, nausea, constipation, and defecatory dysfunction to be significantly more frequent in PD than controls (13, 22). In congruence with prior studies, this study found weight loss, sialorrhea, dysphagia, constipation, and defecatory dysfunction to be significantly more prevalent in PD than controls. Though not statistically significant, the difference in the prevalence of nausea between PD and controls was close to achieving statistical significance ($p=0.06$) within this sample.

The finding of defecatory dysfunction in nearly half of stage 1 patients is very intriguing, and when coupled with the results of the factor analysis that suggests that defecatory dysfunction may have a significant impact on quality of life, it suggests that this symptom may be a much more common and important manifestation of GI dysfunction in PD than previously recognized. Unfortunately, no known effective

treatments exist for defecatory dysfunction in PD, making this a prime target for future clinical trials. Though known to occur frequently in PD, this study is the first to document the high prevalence in the earliest stages of disease (13).

There is a paucity of data on the treatment of GI symptoms in PD. Data from this study on symptomatic GI medication usage can be used to help determine which agents, or combinations of agents, to use in future treatment trials. This medication data suggests that PD patients can have a poor response to commonly used GI medications, underscoring the need for disease-specific treatments.

This study had limitations in its design. First, a cross-sectional study design is sub-optimal for a study intended to explore the relationship between the GI and motor manifestations of PD, which would most ideally be accomplished by following a cohort prospectively as they advance through the H&Y stages of disease. Given that PD progresses very slowly over approximately 20 years, longitudinal studies of PD are protracted and cumbersome. This cross-sectional approach was thus selected. Secondly, because the GIND only covers the 2 weeks prior to survey (to avoid recall bias), the temporal relationship between GI and motor symptom manifestation was uncertain, making a case-control analysis impossible. Therefore, H&Y stage was used as a proxy for time and the cross-sectional dataset was analyzed as a cohort study. Thirdly, data on diet and physical activity were not collected. Thus, these potentially important variables were not controlled for in the analysis. The use of spouses as controls was intended to minimize the effects of dietary and lifestyle factors in the analysis; however, use of spouses as controls led to other imbalances between the groups (e.g. age and sex) which could have induced bias into the study design. However, the size and direction of this

potential bias was probably insignificant. Age was only weakly correlated with GIND scores in this dataset; therefore, it is unlikely that the 4 year difference in mean age between cases and controls induced a significant bias. There were significantly more women in the control group, and there are data in the medical literature to suggest that women experience more GI symptoms than men. Therefore, the direction of the bias induced by this gender imbalance likely made rejecting the null hypothesis more difficult.

This study was also limited by its small sample size. Due to low sample size in the akinetic-rigid and tremor-predominant groups, motor phenotype could not be retained in the final model. Greater numbers of subjects would enable incorporation of motor phenotype into the model in order to determine if the relationship between H&Y stage and GIND total score differs between the 3 motor phenotypes. This is an interesting and relevant question given the differences in overall mobility between the 3 motor phenotypes, which could potentially influence the expression of certain GI symptoms like constipation.

Because of the lack of racial heterogeneity at our institution, race could not be included as a variable in the model. Epidemiological studies have suggested that the incidence of PD may indeed vary by race. One recent US study found the incidence of PD to be highest among Hispanics, followed by non-Hispanic Whites, Asians, and Blacks (23). This is, therefore, another limitation of this study, as the sample does not accurately reflect the racial diversity of the PD population. Furthermore, there may be important differences in GI symptom expression across the races.

The GIND is a much-needed and very promising new tool for the study GI symptoms in PD. However, it had not been previously piloted and all quantitative tests of its validity and reliability reported herein were performed on this pilot dataset. Moving forward, the GIND needs to be administered in other populations to better assess its validity and reliability. The skewed GIND scores suggest that the scale may not yet be optimally calibrated for use in this population; however, the sample was heavily weighted toward early stage patients, which could explain the significantly skewed scores. More data from advanced stages is needed to clarify this issue.

Despite these limitations, this study has numerous strengths, including the creation and use of a novel scale for GI symptoms in PD. Only one other group has rigorously evaluated the relationship between H&Y stage and GI symptoms, and this study improves upon their work by incorporating more patients with H&Y stage 1 disease and by controlling for relevant confounders in the analysis. This study was the first to report prevalence data on individual GI symptoms by H&Y stage. Thus, this study adds important information to the small body of literature on the GI symptoms in PD and will serve to motivate future studies.

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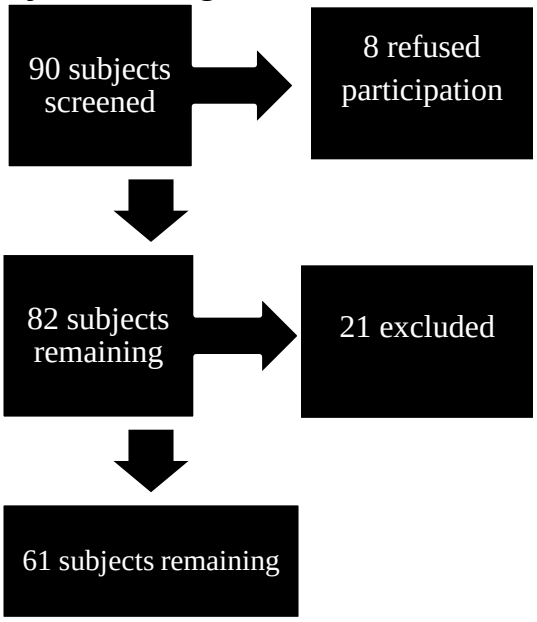
Figure 1. Subject screening and enrollment



Reasons for Exclusion:

9 with alternative causes of Parkinsonism (2 DLB, 4 PSP, 1 MSA, 1 DIP, 1 psychogenic)

2 with unconfirmed PD diagnosis *

1 treated with DBS

4 with no spouse

5 with GI disturbance from another known cause in either patient or spouse

-1 colostomy (patient)

-1 ulcerative proctitis (spouse)

-1 ulcerative colitis (patient)

-1 Crohn's disease (patient)

-1 Crohn's disease (spouse)

DLB= Dementia with Lewy Bodies

PSP= Progressive Supranuclear Palsy

MSA= Multiple Systems Atrophy

DIP= Drug-induced Parkinsonism (from Valproate)

DBS= Deep brain stimulation surgery

*Patients enrolled at support group meeting who had never been seen at our medical center

Figure 2: Distributions of GIND total score by group

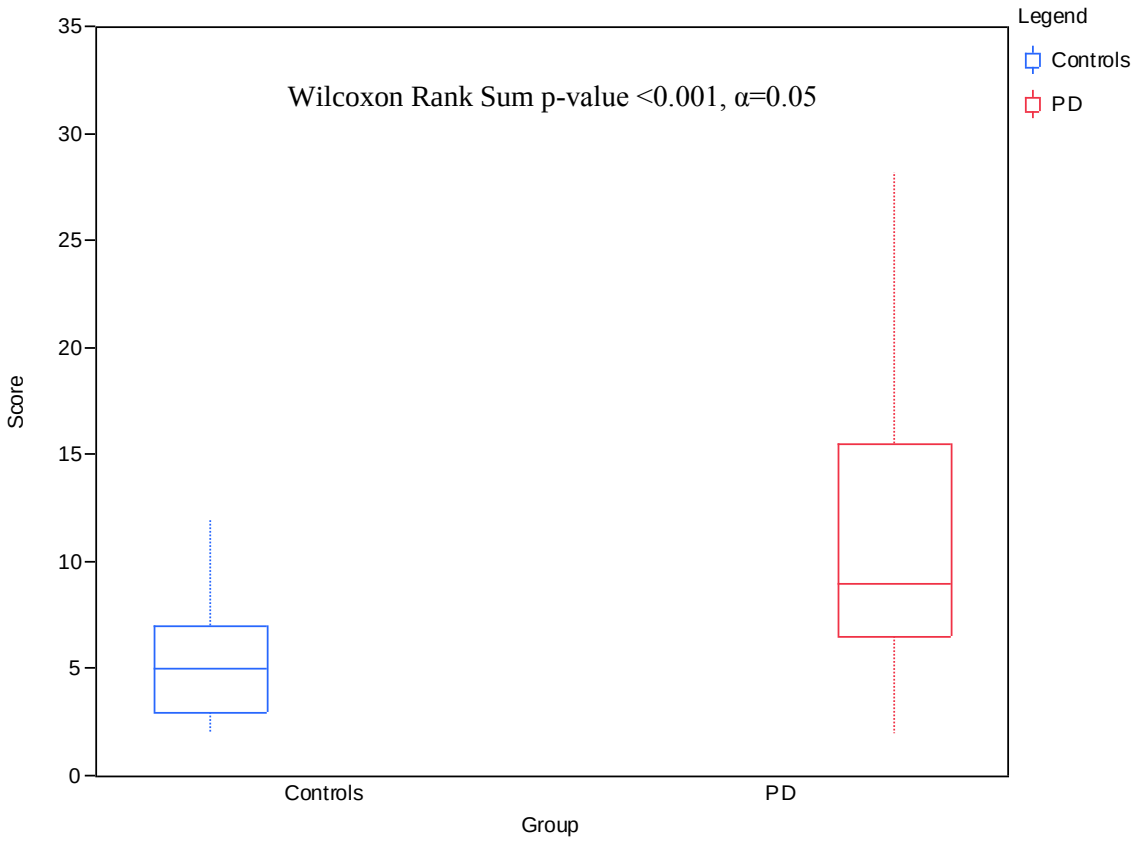


Figure 3: Distributions of GIND total score by H&Y stage

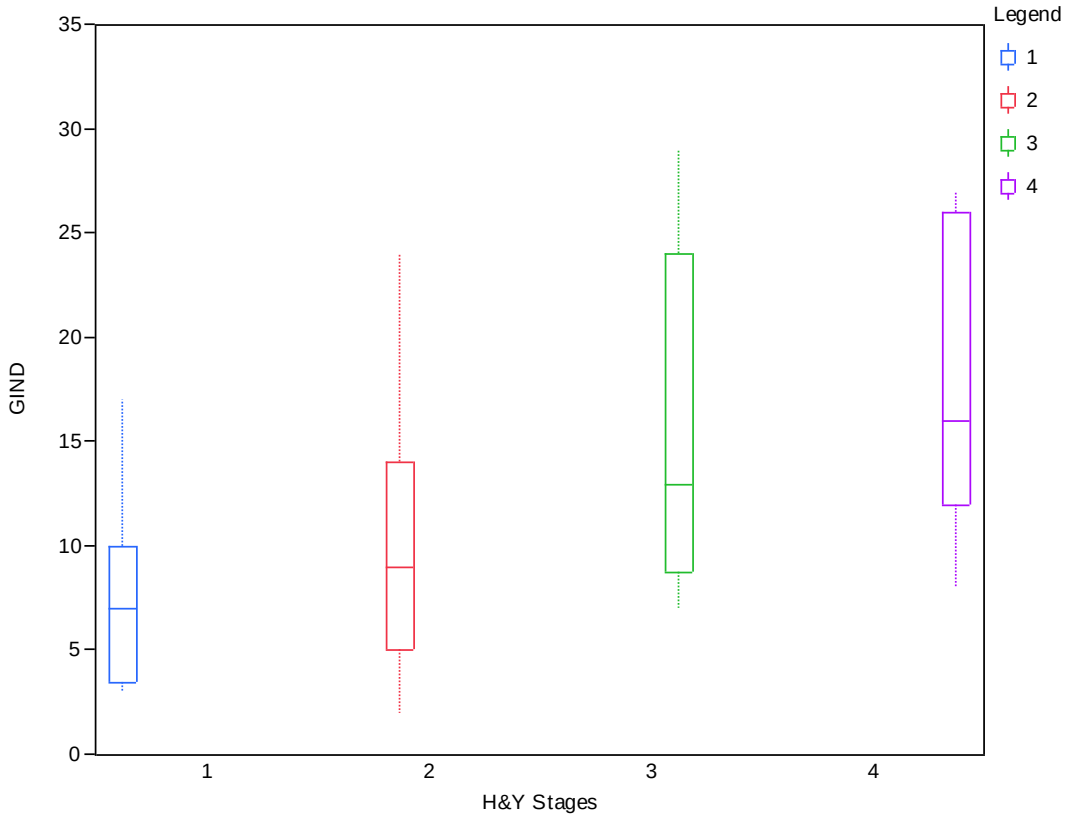


Figure 4: Mean Ln GIND total score in PD stages 1-4 and their matched controls

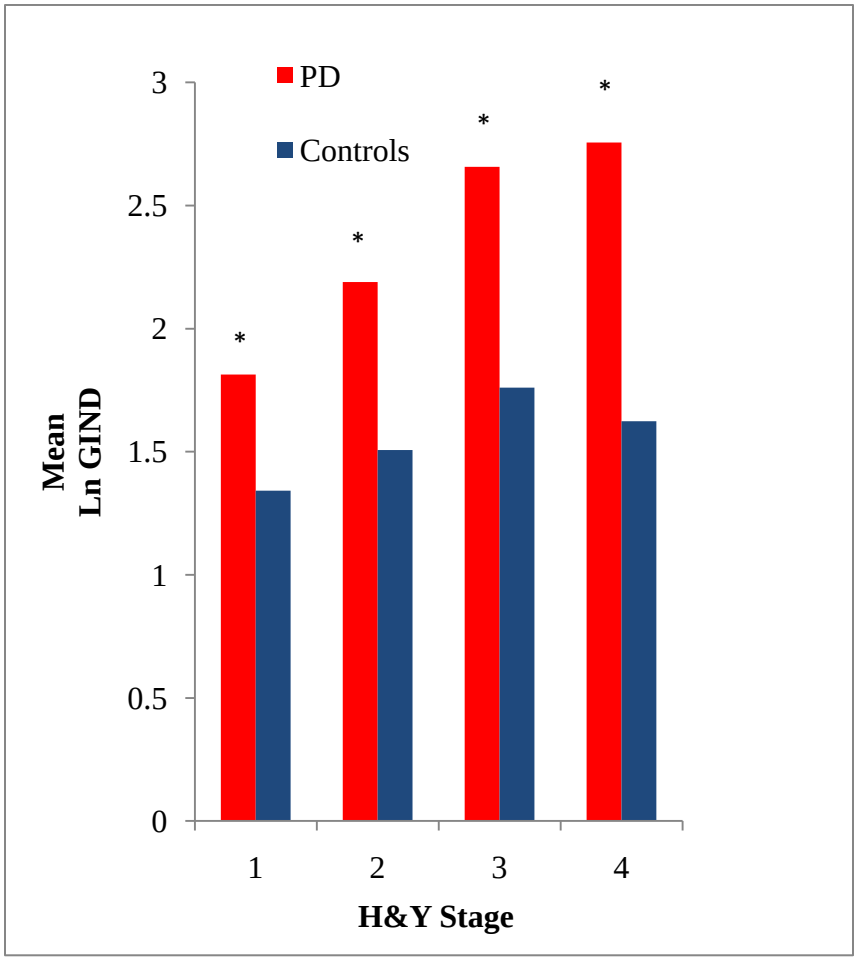


Figure 5: Prevalence of GI symptoms by H&Y stage

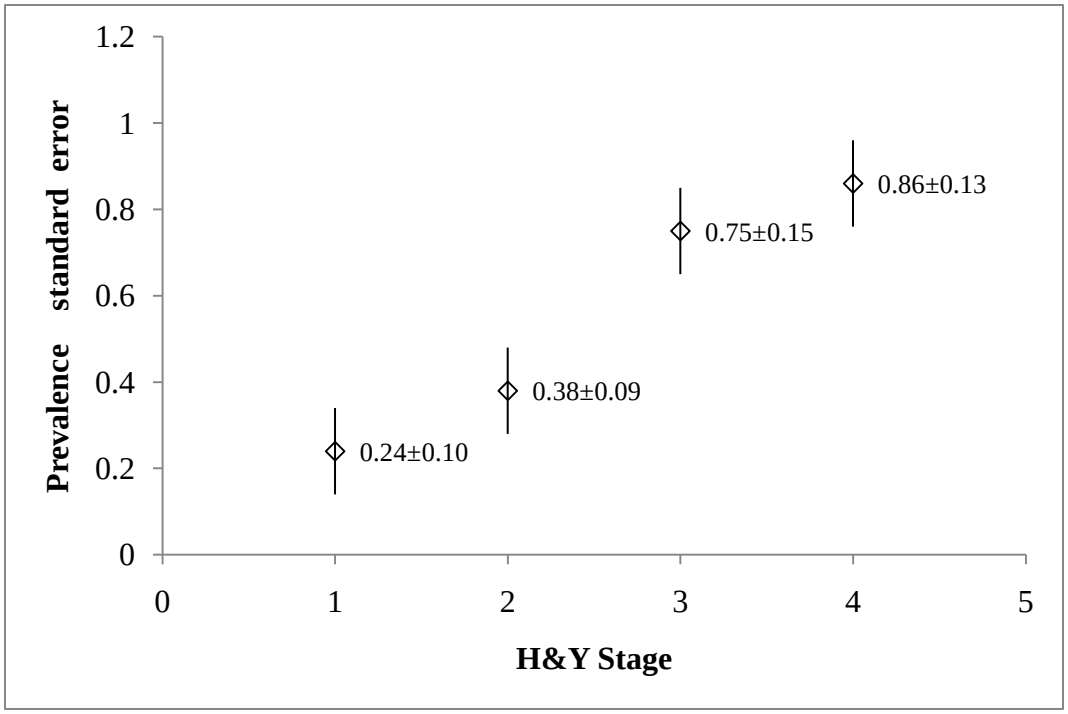


Figure 6: Use of symptomatic GI medications by H&Y stage

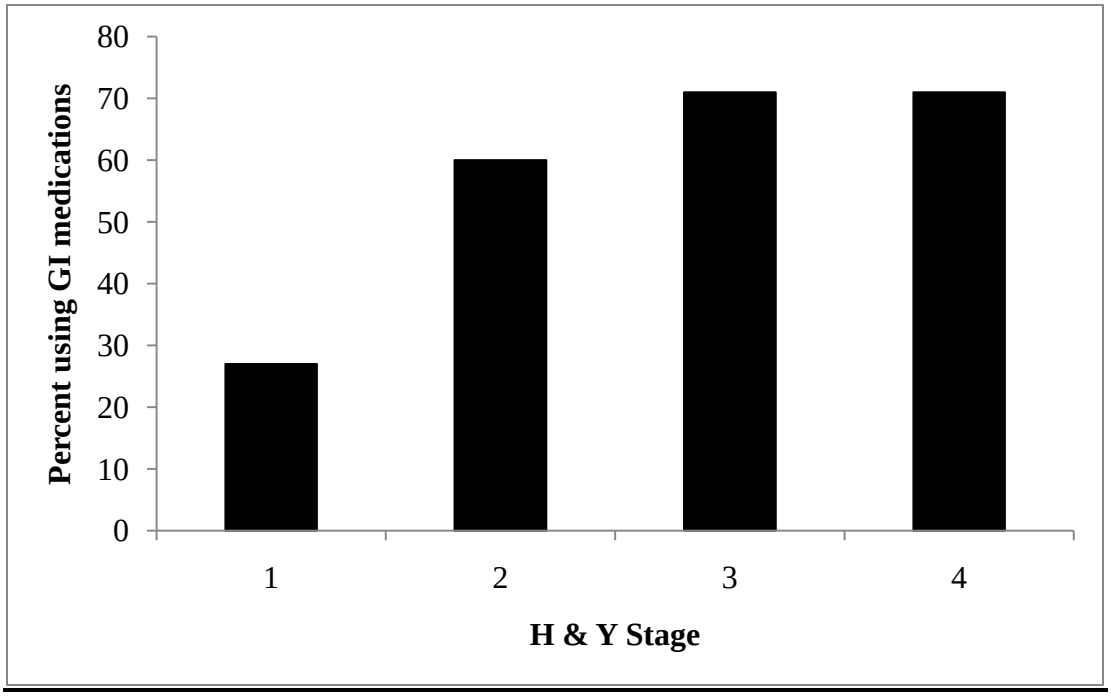


Table 1: Baseline characteristics of study subjects

	PD N=61	**Controls** N=61	P-value*
Age in Years Mean ± Std Dev	66.6 ± 8.4	62.8 ± 10.3	0.026
Sex N (%)	Male= 41 (67) Female= 20 (33)	Male= 21 (34) Female= 40 (66)	0.0003
Race N (%)	Caucasian= 60 (98) AA= 1 (2)	Caucasian= 60 (98) AA= 1 (2)	
H&Y Stage N (%)	Stage 1= 17 (28) Stage 2= 29 (47) Stage 3= 8 (13) Stage 4= 7 (12)		
Motor Phenotype N (%)	Classic Mixed= 44 (72) Akinetic Rigid= 6 (10) Tremor Predominant= 11 (18)		
Disease Duration in years Mean ± Std Dev	6.35 ± 4.16		

*P-value calculated by Pooled 2 sample T-test for age and Pearson's χ^2 for sex, 2-sided p value calculated at alpha=0.05.

Table 2: Two-way ANOVA evaluating the effects of H&Y stage and group on LnGIND

Source	DF	Sum of Squares	Mean square	F value	P value
Stage (H&Y 1-4)	3	5.25	1.75	4.59	0.005
Group (PD vs. Control)	1	14.9	14.9	39.2	<0.0001
Stage*Group	3	0.910	0.300	0.800	0.498

Bonferroni posttests for PD vs. Control

H&Y stage	Difference (PD vs. Control)	95% CI of difference	P value
1	0.576	0.038-1.11	<0.05
2	0.681	0.269-1.09	<0.001
3	0.896	0.113-1.68	<0.05
4	1.13	0.294-1.97	<0.01

Table 3: Statistical evaluation of the frequency of individual GI symptoms in PD patients vs. controls

Variable	Cases		Controls		$\chi 2$	p-value*
	n	%	n	%		
Nausea	7	12	1	2	X	0.06**
Vomiting	1	2	0	0	X	1.0
Anorexia	3	5	1	2	X	0.62**
Dysphagia	13	21	2	3	X	0.0044**
Sialorrhea	20	33	0	0	X	3.0E-7**
Early satiety	12	20	3	5	X	0.025**
Bloating	19	31	10	16	3.66	0.056
Constipation	27	44	13	21	7.29	0.0069
Abdominal Pain	7	12	3	5	X	0.32**
Gas	28	46	20	33	2.198	0.14
Defecatory Dysfunction 1	15	25	3	5	X	0.0039**
Defecatory Dysfunction 2	31	51	8	13	19.94	8.0E-6
Weight Loss	9	15	0	0	X	0.0028**

Defecatory Dysfunction 1= Feeling of having to go to the bathroom even though your bowels are empty

Defecatory Dysfunction 2= Problems with defecation (excessive straining, pain, or a feeling of incomplete evacuation

α=0.05

** Fishers' Exact Test

*Two-tailed p-value

Table 4: Percent of individual GI symptoms observed in the H&Y stages of PD

Variable	Stage 1	Stage 2	Stage 3	Stage 4
Nausea	12	10	13	14
Vomiting	0	0	0	14
Anorexia	6	3	0	14
Dysphagia	6	10	50	71
Sialorrhea	12	28	88	43
Early satiety	6	24	25	29
Bloating	29	28	50	29
Constipation	47	35	50	71
Abdominal Pain	12	14	13	0
Gas	35	38	75	71
Defecatory Dysfunction 1	18	17	38	57
Defecatory Dysfunction 2	41	52	50	71
Weight Loss	0	17	13	43

Defecatory Dysfunction 1= Feeling of having to go to the bathroom even though your bowels are empty

Defecatory Dysfunction 2= Problems with defecation (excessive straining, pain, or a feeling of incomplete evacuation

Table 5: Laxative use

	PD	**Controls**	**P value***
≥1 daily med for constipation N (%)	23 (38)	5 (8)	0.0002
Stool softeners (%)	12	2	
Bulk-forming (%)	15	5	
Osmotic (%)	13	0	
Stimulant (%)	5	3	

*Fisher Exact test, α=0.05

Table 6: Final model

Variable	Parameter estimate	Standard Error	P-value
Age (continuous)	0.006	0.011	0.594
Sex (dichotomous)	0.134	0.180	0.461
Dopaminergics (dichotomous)	-0.208	0.277	0.456
Stage 2 vs 1*	0.226	0.203	0.269
Stage 3 vs 1*	0.678	0.295	**0.025**
Stage 4 vs. 1*	0.756	0.305	**0.016**

*Design variables representing the 4 H&Y stages included in the sample

Table 7: ANOVA table for final model

Source	DF	Sum of Squares	Mean Square	F value	P value
Model	6	5.84	0.973	2.33	0.0449
Error	54	22.5	0.417		
Corrected Total	60	28.4			

Root MSE	0.646	R-square	0.206
Dependent Mean	2.24	Adj R-sq	0.118
Coeff Var	28.9		

Appendix 1: Hoehn & Yahr scale

Stage One
- Signs and symptoms on one side only
- Symptoms mild
- Symptoms inconvenient but not disabling
- Usually presents with tremor of one limb
- Friends have noticed changes in posture, locomotion and facial expression

Stage Two
- Symptoms are bilateral (on both sides)
- Minimal disability
- Posture and gait (walking) affected

Stage Three
- Significant slowing of body movements
- Early impairment of equilibrium on walking or standing
- Generalized dysfunction that is moderately severe

Stage Four
- Severe symptoms
- Can still walk to a limited extent
- Rigidity and bradykinesia (stiffness and slowness)
- No longer able to live alone
- Tremor may be less than earlier stages

Stage Five
- Cachectic stage (significant weight loss)
- Invalidism complete
- Cannot stand or walk
- Requires constant nursing care

Appendix 2: Factor Analysis

Methods

Initially, the factorability of the 13 GIND items was examined. Multiple well-recognized criteria for determining factorability were used. First, 12 out of the 13 items correlated at least 0.3 with at least one other item, suggesting reasonable factorability. Second, the Kaiser-Meyer-Olkin measure of sampling adequacy was 0.79, which is above the recommended value of 0.6. Lastly, the communalities for 11 of the 13 items were above 0.3, further confirming that the majority of the items shared some common variance with other items. Iterated principal factor analysis was used because the primary objective was to determine the number of latent constructs within the GIND. Orthogonal (VARIMAX) rotation was used to create a factor structure in which each variable loads highly on one and only one factor, thereby assuring that each factor will represent a distinct construct. Kaiser's criterion (eigenvalue-greater-than-one rule) along with Cattell's scree test were used to determine the number of factors needed to explain the correlations among the variables. Results were deemed interpretable because all items had significant loadings (>0.3), variables on the same factor share conceptual meaning, and the rotated factor pattern demonstrates a simple structure (high loadings on one factor with low loadings on the other factors) for 11 of the 13 variables. Results are summarized in the following table.

Appendix 2, Table 1: Primary factor loadings and communalities based on a factor analysis with VARIMAX rotation for the 13 GIND variables

	Factor 1: Distal gut dysfunction	Factor 2: Symptoms influenced by overall mobility	Factor 3: Gastroparesis	Communality
Variance explained by each factor	3.1	1.4	1.3	
Cronbach's alpha for each factor	0.81	0.52	0.48	
Nausea			0.49	0.38
Vomiting			0.55	0.48
Anorexia			0.54	0.31
Dysphagia		0.55		0.44
Sialorrhea		0.53		0.39
Early satiety	0.62			0.66
Bloating	0.71			0.52
Constipation		0.46		0.22
Abdominal pain	0.82			0.70
Impact on QOL	0.65			0.46
Excessive gas	0.45			0.23
Defecatory dysfunction 1	0.60			0.47
Defecatory dysfunction 2	0.50			0.47

Defecatory Dysfunction 1= Feeling of having to go to the bathroom even though your bowels are empty

Defecatory Dysfunction 2= Problems with defecation (excessive straining, pain, or a feeling of incomplete evacuation

Interpretation

Factor 1: Many nonspecific symptoms that reflect distal gut dysfunction (defecatory dysfunction, abdominal pain, excessive gas, bloating, and early satiation) load most heavily onto factor 1. Interestingly, the variable pertaining to quality of life loads most heavily onto this factor, suggesting that these symptoms may be most bothersome to patients.

Factor 2: Dysphagia and sialorrhea are the result of inefficient swallowing due to dysfunction of oropharyngeal musculature in PD patients, which tends to occur in later stages of disease when patients become moderately to severely akinetic. Constipation, which we defined by low frequency of bowel movements, can also be strongly influenced by overall mobility, often becoming more severe in more advanced PD when patients are significantly akinetic.

Factor 3: Nausea, vomiting and anorexia, which all result from underlying gastroparesis, load most heavily onto factor 3.

Appendix 3. Distribution of GIND and Ln GIND