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Cross-Sectional Study: Prevalence of Gastrointestinal Symptoms in Early-Stage Parkinson's Disease

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Abstract

Background: Parkinson's Disease (PD) is a progressive neurological condition characterized by degeneration of dopaminergic neurones within the basal ganglia. Accruing evidence from a variety of different studies suggests pathophysiological changes may first originate in the gut before they become apparent within the brain. The aim of the study was to investigate the prevalence of Gastrointestinal Tract symptoms (GIT) of early-stage PD patients. As such, this research aims to provide further supporting evidence to this limited field.

Methods: A single-center cross-sectional study conducted over 4 months which followed 12 participants with early-stage PD and 9 healthy controls. Participants completed a PD-specific gastrointestinal symptom questionnaire. Disease progression was evaluated through the Hoehn and Yahr Scale and Unified Parkinson's Disease Rating part III (UPDRS) motor score.

Results: Tenesmus (83.3%), constipation (58.3%) and abdominal bloating (58.3%) were the most experienced symptoms for early-stage PD patients. Tenesmus (p=0.006) and constipation (p=0.03) also showed statistically significant differences between PD and control groups. However, there was no significant relationship between the prevalence of gut symptoms and UPDRS motor score (r=0.278, p=0.38).

Conclusion: A variety of gastrointestinal symptoms, particularly lower gastrointestinal tract, were prevalent in early-stage disease. There was no apparent relationship between the prevalence of gastrointestinal tract symptoms and the UPDRS motor score. A well designed, appropriate gastrointestinal tract questionnaire to screen for symptoms in early-stage disease may be of use in future clinical practice.

Keywords: Parkinson's disease; Gastrointestinal symptoms; Brain

Introduction

Parkinson's disease is a progressive neurological condition characterized by motor impairment. Predisposing to these motor symptoms is the degeneration of dopaminergic neurons within the basal ganglia [1]. Over the last 15 years, there has been a growing consensus within the scientific community that an inherent link involving the brain and the gut exists. First proposed by Braak, et al. a change in the healthy synergistic microbial composition of the gut to a more pathogenic profile may lead to aggregation of α-synuclein enriched Lewy bodies. These Lewy bodies then transcend up the nervous system and deposit within the dopaminergic neurones of the brain, leading to neocortical changes [2].

It is clear patients suffer from a variety of GIT symptoms [3,4]. However, few studies have estimated the prevalence and severity of GIT symptoms in early-stage disease. As per Braak's hypothesis, if GIT symptoms are present in the early stages, it may firstly be used to identify patients in the prodromal stages and secondly perhaps provide a clearer indication of the disease progression.

This study aims to provide evidence to the body of information supporting the development of PD from within the GIT and further add to the limited studies aimed at investigating the prevalence of these symptoms in the early stages of the disease. Building and researching this topic further could be imperative as it may lead to earlier diagnosis with new and improved treatments for patients.

Methods

Patients were recruited from the Neurology Clinics in a tertiary care centre in Norfolk, United Kingdom. Potential participants were screened during their clinic appointment with suitability based on the clinical history, disease staging and eligibility for the study. Participants aged between 50 and 90 years old who fit the inclusion and exclusion criteria (Table 1) were included in this study. All participants in the patient group had a clinical diagnosis of PD and all patients selected were on some form of medication treatment for their PD. The study was approved by the national ethics committee and all subjects involved provided informed consent.

Inclusion criteria	Exclusion criteria
• Aged between 50 and 90 years old • Have a clinical diagnosis of Parkinson's disease and a cohabitant who is willing to participate in the study • Male and female • No significant comorbidities which would prevent participation in the study • Willing and able to provide written informed consent, including full mental capacity • Fluent in written and spoken English. • Normal or corrected to normal vision and hearing • Understands and is willing and able to comply with all study procedures	• Significant memory complaints or a diagnosis of dementia • History or MRI evidence of brain damage, including significant trauma, stroke, learning difficulties or serious neurological disorder, including a loss of consciousness for more than 24 hours • Metabolic diseases such as liver disease, diabetes mellitus etc., which affects the gastrointestinal tract and associated microbiota • History of alcohol or drug dependency. • Clinically diagnosed psychiatric disorder. • Any significant medical condition likely to affect participation • Currently a participant or have been a participant in any other study involving an investigational product within the last 4 weeks • The absence of a cohabitant to be a study partner

Table 1: Inclusion and Exclusion Criteria.

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Clinical assessments firstly involved the Hoehn and Yahr scale [5] to recruit patients in the early-stages of their disease. A common validated scale used to measure the progression of Parkinson's symptoms and the level of disability, early-stage was defined as any patient diagnosed with PD and a Hoehn and Yahr Stage of I or II. Stage I was defined as symptoms on one side only (unilateral) and Stage II was defined as symptoms on both sides (bilateral) but with no impairment of balance.

The Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [6] is a common validated scale used to follow the longitudinal progression of PD. It consists of 5 different scales which together provide a comprehensive evaluation of the condition. For this study, we used Part III of the UPDRS, the evaluation of motor function. An 18-point examination was completed by a consultant neurologist in an outpatient clinic setting, each item was rated from 0 to 4 where 0=normal, 1=slight, 2=mild, 3=moderate, and finally 4=severe.

In order to assess the prevalence of gastrointestinal symptoms, the gastrointestinal symptom rating scale was used [7]. Normally used for IBS and dyspepsia, this questionnaire was modified from 15 to 8 symptoms to make it more PD relevant. The symptoms removed were: Nausea and Vomiting, Abdominal Rumbling, Abdominal Sucking Sensations, Eructation or Belching, Flatus, Diarrhoea, Acid Regurgitation and Increased Passage of Stools. Dysphagia, a common PD symptom, was added to our list of symptoms which included Constipation, Tenesmus, Gastro-Oesophageal Reflux, Abdominal Pain, Abdominal Bloating, Early Satiety and Stool Consistency. Each symptom was scored from either the severity or the frequency of the symptom, with each scale ranked from 0 to 3. The total score was calculated by adding all the scores together, therefore the maximum score for any one participant was 24.

Statistical analysis

The software programme G*Power 3.1 was utilised to calculate our sample size. Based on a similar study which investigated the prevalence of GIT symptoms in PD [8], we required at least 8 participants per group to detect a significant effect. This was under the assumption of 95% power for a one-sided α-level of .05, a mean gastrointestinal rating score of 25.43 and a standard deviation of 18.62. Demographic and biological data were analysed using the Statistical Package for the Social Sciences (SPSS; v25.0), applying standard statistical thresholds ($p<0.05$), corrected for multiple comparisons where appropriate. Correlational, multi-variate and multi-level regression analyses were used to examine relationships between GIT symptoms and clinical information.

Results

Cohort description

For this study, we recruited a total of 21 participants, 12 early-stage PD patients and 9 controls (Table 2). The mean age for PD and controls was 70.7 ± 4.8 and 70.7 ± 6.6 years, respectively. PD group consisted of 8 males and 4 females with every participant in each group of White British ethnicity. For PD patients, the mean Hoehn and Yahr stage was 1.6 ± 0.5, mean motor UPDRS score was 25.3 ± 12.2 and mean duration since diagnosis was 31.7 ± 27.3 months. Finally, PD and control BMI (kg/m^2) were 26.1 ± 5.8 and 29.8 ± 5.7. However, one participant from each group declined to provide information for height and weight and therefore we were unable to calculate BMI.

Variable	Parkinson's Disease (n=12)	Control (n=9)
Age, years (mean ± SD)	70.7 ± 4.8	70.7 ± 6.6
Gender	1 month	1 month
Male	8	3
Female	4	6
Hoehn and Yahr Scale	1.6 ± 0.5	
Motor UPDRS Score	25.3 ± 12.2	
Mean Duration (months)	31.7 ± 27.7	
Ethnicity	1 month	1 month
White	12	9
Asian or Asian British	0	0
Black or Black British	0	0
Mixed	0	0
Other	0	0
BMI, kg/m^2 (mean ± SD)	26.1 ± 5.8	29.8 ± 5.7

Table 2: Patient Baseline Characteristics (n=21).

All participants completed the PD-specific gastrointestinal tract questionnaire. For the PD group, the most common symptoms experienced by patients were the following: tenesmus (83.3%), constipation (58.3%), bloating (58.3%), reflux (50%), abdominal pain (41.7%), and hard stools (50%). Early satiety (16.7%) and dysphagia (8.33%) were experienced by the fewest number of patients. Tenesmus ($p=0.006$) and constipation ($p=0.03$) were the only symptoms to show statistically significant differences between PD and control groups. Binary logistic regression tests were used to determine the odds ratios for the prevalence of gastrointestinal symptoms between the two groups (Table 3). Tenesmus was the only GIT symptoms in PD did not correlate with age or gender. Amongst symptoms, a strong positive correlation was only observed between constipation and hard stools ($r=0.708$, $p<0.001$). PD duration correlated with early satiety ($r=-0.588$, $p=0.04$), but with no other GIT symptom.

Each gastrointestinal tract symptom was ranked by participants on a scale from 0 to 3 concerning either the frequency or the severity. The total GSRS mean scores for the Parkinson's disease and control groups was 5.75 ± 3.36 and 2.22 ± 3.38, respectively. The total median GIT symptoms score for PD and Control was 7.0 (IQR 2.25 to 8.75) and 1.0 (IQR 0.0 to 4.50). These median results between the two groups were statistically significant too ($p=0.02$).

The mean scores for each gastrointestinal symptom are listed in Table 4. For PD patients, constipation, hard stools and tenesmus each had the highest mean frequency and severity score with 1.25. The highest mean scores for controls were reflux (0.67) and bloating (0.44).

Gastrointestinal tract symptoms	Frequency PD (n) (%)	Frequency Controls (n) (%)	OR (95% CI)	P Value
Tenesmus	10 (83.3)	2 (22.2)	17.5 (1.97-155.6)	0.01
Constipation	7 (58.3)	1 (11.1)	11.20 (1.04-120.36)	0.05
Abdominal Pain	5 (41.7)	1 (11.1)	5.71 (0.53-61.40)	0.15
Bloating	7 (58.3)	2 (22.2)	4.90 (0.70-34.30)	0.11
Hard Stools	6 (50.0)	3 (33.3)	2.00 (0.33-11.97)	0.45
Early Satiety	2 (16.7)	1 (11.1)	1.60 (0.12-21.0)	0.72
Reflux	6 (50.0)	4 (44.4)	1.25 (0.22-7.08)	0.8
Dysphagia	1 (8.33)	0 (0.00)	0	1

Table 3: Prevalence and Odds Ratios for Gastrointestinal Symptoms between PD and Control groups.

Gastrointestinal tract symptoms	PD	Control
Abdominal Pain	0.45 ± 0.52	0.22 ± 0.67
Bloating	0.83 ± 0.94	0.44 ± 0.73
Constipation	1.25 ± 1.22	0.22 ± 0.67
Hard Stools	1.25 ± 1.29	0.33 ± 0.50
Early Satiety	0.17 ± 0.39	0.33 ± 1.00
Dysphagia	0.08 ± 0.29	0.11 ± 0.33
Tenesmus	1.25 ± 0.87	0.22 ± 0.44
Reflux	0.58 ± 0.67	0.67 ± 1.00
Total	5.70 ± 3.59	2.50 ± 3.51

Table 4: Mean Gastrointestinal Tract Symptoms frequency and severity in PD and Control Groups.

Pearson's Correlation test was used to determine the association between the total gastrointestinal symptoms questionnaire score and the UPDRS motor score. A weakly positive correlation was present (r=0.278), however, the result was not statistically significant (p=0.38).

Of the PD participants recruited for this study, 5 had Stage I and 7 had Stage II disease. The mean Hoehn and Yahr scale for participants was 1.58 ± 0.52. Patients with Stage I reported symptoms as follows: tenesmus (80%), constipation (80%), hard stools (80%), bloating (60%), early satiety (40%), reflux (40%) abdominal pain (20%) and dysphagia (0%). Stage II participants reported all symptoms, but most common were tenesmus (85.7%), reflux (57.1%), abdominal pain (57.1%) and bloating (57.1%).

Discussion

The results from this study show that patients with early-stage PD suffer from a variety of different gastrointestinal tract symptoms. Early-stage PD patients showed an increased prevalence of lower gastrointestinal tract symptoms, in particular, tenesmus, constipation and hard stools. These findings complement the one previous study investigating symptoms in the early stages [8]. Our results also displayed the odds of having tenesmus in PD compared with controls was 17.5 times more likely, whist a strong positive correlation between constipation and hard stools was also observed. These reported lower GIT symptoms may arise from abnormal physiological processes involving the large colon. In the early-stages of the disease, degeneration of the enteric nervous system has been observed. This is a significant finding, the ENS is fundamental in regulating smooth muscle activity and intestinal peristalsis, with a couple of papers demonstrating increased mean colonic transit times [9,10]. Aside from the delay in GI transit time, the coordination of perianal muscles is also important in the role of defecation. Confirmed through anorectal manometry and defecography studies, atypical contraction of the puborectalis and impaired relaxation of anal sphincter muscles may prevent defecation leading to an outlet obstruction [11,12]. This obstruction might lead to the feeling of incomplete evacuation, but also extra GIT manifestations including abdominal pain and bloating. Another aspect is the emergence of Lewy body findings within the large colon and the ENS [10,13]. This is noteworthy as there may be a causative link between the presence of Lewy bodies, lower GIT symptoms and the associated physiological gut changes. Interestingly, both Lebouvier et al. and Sanchez-Ferro, et al. found an increased prevalence of chronic constipation patients with Lewy pathology [14,15]. Further assessment must be done to identify the role of Lewy pathology and the association with GIT symptoms.

Upper gastrointestinal tract symptoms including dysphagia and early satiety were less common in the early stages of the disease; however, acid reflux was experienced by half of the PD cohort. Notably, the previous study completed by Su, et al. did not necessarily match our findings. Their study results exhibited a higher prevalence of dysphagia (29.6%), equal prevalence for early satiety (16.7%) and a lower prevalence for acid reflux (7.4%). Swallowing issues have been detected in the earliest stages of the disease with oesophageal manometry and barium studies confirming abnormal swallowing patterns involving each of the three phases of deglutition [16,17]. Interestingly, the final phase of swallowing i.e. the oesophageal phase in which aperistalsis and oesophageal spasms have been observed is under autonomic control by the oesophageal myenteric plexus [18]. Here, Lewy bodies have been visualised under histopathological analysis which suggests dysphagia could arise from damage to the enteric nervous system. Moreover, we noticed a strong positive correlation between abdominal pain and acid reflux. Abdominal pain, experienced by 41.7% of PD patients in our study, is considered an atypical manifestation of acid reflux and so it remains open whether the reported abdominal pain is a sign of reflux or PD.

Our study was also unable to identify a relationship concerning either the prevalence or the severity of GIT symptoms with the Hoehn and Yahr Scale staging. As found by one previous studies [19], we expected patients with Hoehn and Yahr Stage 2 to have an increased variety and prevalence of symptoms compared with Stage 1. Moreover, no statistically significant correlation was apparent between the UPDRS score and the total GIT questionnaire score. The UPDRS indicates disease severity and so it was expected this would correlate with an increased GIT questionnaire score-maybe with a larger volume of patients this may become more apparent Finally, there was also no relationship between the duration of PD since diagnosis and the total GIT prevalence score, however, we surprisingly noticed a strong negative correlation between duration and early satiety. It is an interesting concept that the longer a patient has PD the likelihood of having early satiety is lowered. Perhaps this may be due to a change in diet or simply better treatment and management of the condition. Early satiety was also associated with hard stools which could imply nutrition i.e. low fibre foods as a causal factor.

Study limitations

Despite these promising findings, the study has several limitations. Firstly, despite meeting our power calculation, ideally we would have recruited a high volume of patients and therefore recommend a study with a larger sample from both PD and control populations. Secondly, the cross-sectional nature of the study could be considered a limiting factor. We collected data at one moment of time and therefore unable to establish a cause and effect relationship. Ideally, a prospective cohort study over a lengthened period would be suitable to calculate risk and identify any factors which predispose to PD. Thirdly, bias could arise from the unequal distribution of confounding factors and participant self-reporting. Finally, all participants for our study were of White British ethnicity which is expected due to the ethnic composition of Norfolk, as a result, this may reduce the generalisability of the findings.

Conclusion

To summarise, patients with early-stage PD suffered from a variety of gastrointestinal tract symptoms with reported increased prevalence of lower gastrointestinal tract compared with the upper gastrointestinal tract. These results could suggest a possible pathophysiological link seen within the gut and in particular with Braak's hypothesis. We recommend further assessment of GIT symptoms involving the timing of symptoms in relation to the onset of diagnosis. We also propose all patients in the early-stages should be appropriately screened with a GIT questionnaire to allow prompt recognition of symptoms and thus provide effective treatments in the overall management of Parkinson's disease.

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