RESEARCH LETTER

Upper and Lower Gastrointestinal Symptom Association and Duration Preceding Parkinson's Disease

Parkinson's disease (PD) is a complex, multisystem neurodegenerative disorder. While diagnosis and treatment of PD have primarily focused on motor symptomatology, non-motor symptoms (NMS) have become an evolving area of research for earlier diagnosis and treatment. Gastrointestinal (GI) NMS are particularly prevalent, underscoring Braak's hypothesis[1] that PD may spread from the intestine to the brain via the vagus nerve. A 2021 National Institutes of Health workshop highlighted the need for an increased understanding of GI symptoms in PD pathology in view of important knowledge gaps in the onset of GI symptoms prior to diagnosis and gender differences.[2] Previous retrospective studies have evaluated subsets of prodromal GI symptoms (more often, a single symptom, with a particular focus on dysphagia or constipation). However, these analyses rarely examined the timeline in which prodromal GI symptoms precede motor symptom onset—a clinically important addition to the comprehensive and increasing number of evidence-based markers that could allow for initiation of neuroprotective therapies at an earlier stage in PD when therapies might be most effective.[3] They have also often lacked controls, been limited by sample size or recall bias, or did not investigate possible gender differences.[4–9] Therefore, we conducted a case-control study investigating the association and duration of fourteen different upper and lower GI symptoms among men and women prior to PD diagnosis utilizing the medical record.

We assembled a retrospective sample of adult PD patients who presented to the outpatient neurology clinic at Mass General Brigham from 2018 to 2019. Patients were identified using the Research Patient Data Registry. Research Patient Data Registry is a Partners Healthcare electronic database that contains patient billing codes, medications, and encounters.[10] Patients with atypical and secondary Parkinsonism were excluded. Cases were 1:1 matched by age (+/− 3 years), race, and sex with non-PD patients who completed a visit with their primary care physician at Mass General Brigham during the same period. Medical charts were manually reviewed to obtain information on demographics, symptom onset and duration, comorbidities, and PD (or for controls, index) diagnosis dates. Additional details on chart review methods are available in Supplementary Information. Continuous variables were reported as means with standard deviation and compared with *t* tests or Mann-Whitney *U* tests, as appropriate. Categorical variables were reported as frequencies with percentages and compared with Fisher's exact tests. Odds ratios with 95% confidence intervals were calculated (applying Haldane-Anscombe correction to groups with zero patients). Covariates with significance of $P < .05$ in the univariate analysis were entered stepwise into the multivariable model. Multicollinearity was assessed and not detected for the 4 covariates included in the final model by generating a variance inflation factor. Time to diagnosis from GI symptom onset was presented as medians with 95% confidence intervals. Statistical analyses were conducted using R version 4.0.3 (R Project for Statistical Computing) and Prism version 9.4.0 (GraphPad). This study was approved by the Institutional Review Board of Massachusetts General Hospital.

197 patients with PD were matched to 197 controls. Both groups had similar demographic profiles, including similar Charlson Comorbidity Indices (CCI, 3.38 vs 3.63, $P = .118$, respectively), indicating a comparable burden of chronic disease between the 2 groups. Of the fourteen GI symptoms screened, 4 were associated with the subsequent development of PD on univariate screen (Table), including dry mouth (odds ratio [OR] 6.5, 95% confidence interval [CI] 1.47–28.8), dysphagia (OR 5.5, 95% CI 1.22–24.810), heartburn (OR 1.94, 95% CI 1.06–3.54), and constipation (OR 3.4, 95% CI 1.68–6.45). In multivariate analysis, dry mouth (OR 6.22, 95% CI 1.24–31.26) and constipation (3.49, 95% CI 1.19–10.24) were the strongest GI predictors of PD development. Both analyses were adjusted for age, sex, and race. Multivariable analysis was additionally adjusted for dry mouth, dysphagia, heartburn, and constipation.

Significantly associated GI symptoms preceded the onset of PD diagnosis by several years (Figure A1). Heartburn appeared the earliest with a mean of 4.95 (6.04) years prior to PD diagnosis in our study sample, followed by constipation at 3.8 (4.93) years, dysphagia at 1.46 (1.5) years, and dry mouth at 1.36 (1.22) years prior to PD diagnosis. Among PD patients, the Hoen-Yahr scale (a standard instrument describing the progression of PD motor symptoms) and GI symptom occurrence prior to PD diagnosis were similar between sexes (Table A1).

In this case-control study, we identified several upper and lower GI symptoms that are associated with the PD prodromal state as compared to matched controls. Our results suggest the onset of 4 GI symptoms preceding PD diagnosis: dry mouth, dysphagia, heartburn, and constipation. These results corroborate the known association of dysphagia and constipation with prodromal PD,[5] while presenting dry mouth and heartburn as prodromal symptoms that were previously less accounted for and demonstrating the strength of these associations compared to controls. This study also estimates the time by which these 4 symptoms precede PD diagnosis, which has not been widely mentioned

Table. Association Between Parkinson's Disease and Preceding Gastrointestinal Symptoms

	Exposure frequency		Univariate analysis[a]		Multivariable analysis[b]	
	Controls, n (%)	Cases, n (%)	Odds ratio (95% CI)	*P* Value	Odds ratio (95% CI)	*P* Value
Demographics	N = 197	N = 197				
Age (mean, SD)	71.99 (9.01)	71.96 (9.18)	-	.969	N/A	
Race				1	N/A	
White	172 (87.3)	172 (87.3)	-			
Black	11 (5.6)	11 (5.6)	-			
Asian	7 (3.6)	7 (3.6)	-			
Sex (M)	104 (52.8)	104 (52.8)	-	1		
Marital status				.61	N/A	
Single	27 (13.7)	27 (13.7)				
Married or long-term partner	116 (58.9)	129 (65.7)				
Divorced or separated	20 (10.2)	13 (6.6)				
Widowed	23 (11.7)	23 (11.7)				
Unknown	11 (5.6)	5 (2.5)				
Veteran	18 (9.1)	24 (12.2)		.32	N/A	
Charlson Comorbidity Index (mean, SD)	3.38 (1.6)	3.63 (1.7)	-	.12	N/A	
Gastrointestinal symptom						
Dry mouth	2 (1.0)	13 (6.6)	6.5 (1.47–28.8)	**.014**	6.22 (1.24–31.3)	**.027**
Dysphagia	3 (1.5)	12 (6.1)	5.5 (1.22, 24.8)	**.027**	4.83 (0.91–25.7)	.065
Odynophagia	0 (0.0)	1 (0.5)	3.01 (.12–74.5)	.5	-	-
Nausea	21 (10.7)	26 (13.2)	1.31 (0.68, 2.5)	.41	-	-
Vomiting	12 (6.1)	16 (8.1)	1.36 (0.63, 3.0)	.41	-	-
Early satiety	4 (2.0)	4 (2.0)	1.0 (0.25, 4)	1	-	-
Heartburn	21 (10.7)	36 (18.3)	1.94 (1.06, 3.5)	**.03**	1.48 (0.75–2.9)	.26
Abdominal pain	25 (12.7)	40 (20.3)	1.71 (1–2.9)	.05	-	-
Bloating	9 (4.6)	8 (4.1)	0.89 (0.34, 2.3)	.81	-	-
Constipation	15 (7.6)	39 (19.8)	3.4 (1.7, 6.5)	**.0006**	3.49 (1.2–10.2)	**.023**
Straining	1 (0.5)	8 (4.1)	8 (1, 64.0)	.05	-	-
Sense of incomplete defecation	0 (0)	0 (0)	-	-	-	-
Diarrhea	11 (5.6)	20 (10.2)	1.82 (0.87, 3.8)	.11	-	-
Fecal incontinence	2 (1.0)	0 (0.0)	0.20 (0.009–4.2)	.3	-	-

Bold values indicate $P < .05$.
CI, confidence interval; SD, standard deviation.
[a]Analyses reflecting the case-control matching by age, sex, and race. Covariates with $P < .05$ in univariate analyses were entered stepwise into a multivariable model.
[b]Analyses adjusted for age, sex, race, dry mouth, dysphagia, heartburn, and constipation; Hosmer-Lemeshow statistic 3.686, $P = .29$.

with prodromal PD.[2] Furthermore, we present detailed information on the effect of sex on GI symptoms preceding PD, notably demonstrating no significant differences.

This study has strengths and limitations. Our documentation-based approach overcomes the barriers of recall bias in other survey-based studies. However, this form of retrospective chart review may be imperfect if a symptom was never shared with a provider, a provider did not complete a full GI review of systems, or if the true onset of a symptom (or PD diagnosis) was decades prior to the electronic medical record. We suspect this accounts for why our time estimates appear shorter than in other studies.[9] Variable levels of patient interaction with the medical system also affect our results, including possible unaccounted for differences in medication use between cases and controls, despite controlling for the overall degree of illness with the CCI. However, by focusing on prodromal PD, our analysis does avoid capturing the GI side effects of PD therapies. While our study contains a nearly equal male-to-female ratio, which does not reflect the typical male predominance of the general PD population,[11] our analyses were adjusted for sex among other covariates. In terms of generalizability, our results are limited in terms of racial and ethnic diversity, with most study members being non-Hispanic white. Nonetheless, this study is the first controlled study of its size to comprehensively screen for fourteen upper and lower GI symptoms and attempt to understand the time course of these symptoms relative to PD diagnosis.

Overall, this work furthers our understanding of the NMS and early natural history of PD. Our findings also represent the early stages of an opportunity for early recognition by characterizing several symptoms of interest that may raise suspicion for PD development in the correct clinical context. Further research conducted in a prospective manner is needed to better define the chronicity and progression of GI symptoms in PD beyond initial diagnosis. We hope this work can contribute to ongoing efforts[3] for the development and validation of a clinical predictor tool using a pattern of NMS preceding overt motor symptom onset of PD.

S. R. V. GADI[1,2]
J. CHANG[3]
A. VIDENOVIC[4,2]
B. KUO[2,5,‡]
T. S. PASRICHA[2,5,‡]
[1]Department of Medicine, Duke University Health System, Durham, North Carolina; [2]Harvard Medical School, Boston, Massachusetts; [3]Tufts University School of Medicine, Boston, Massachusetts; [4]Department of Neurology, Neurological Clinical Research Institute, Massachusetts General Hospital, Boston, Massachusetts; and [5]Division of Gastroenterology, Department of Medicine, Center for Neurointestinal Health, Massachusetts General Hospital, Boston, Massachusetts

Correspondence:
Address correspondence to: T.S. Pasricha, MD, MPH, Massachusetts General Hospital, Center for Neurointestinal Health, Division of Gastroenterology, 55 Fruit Street, Boston, Massachusetts 02114. e-mail: tpasricha@mgh.harvard.edu.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.12.005.

References

1. Braak H, et al. Neurosci Lett 2006;396(1):67–72.
2. Mawe GM, et al. Gastroenterology 2022;162(6):1574–1582.
3. Hustad E, et al. Front Neurol 2020;11:395.
4. Edwards LL, et al. Mov Disord 1991;6(2):151–156.
5. Chaudhuri KR, et al. Mov Disord 2006;21(7):916–923.
6. Martinez-Martin P, et al. Mov Disord 2007;22(11):1623–1629.
7. Barone P, et al. Mov Disord 2009;24(11):1641–1649.
8. Cersosimo MG, et al. J Neurol 2013;260(5):1332–1338.
9. Savica R, et al. Neurology 2009;73(21):1752–1758.
10. Nalichowski R, et al. AMIA Annu Symp Proc 2006;2006:1044.
11. Balestrino R, et al. Eur J Neurol 2020;27(1):27–42.

‡Co-senior authors.
Abbreviations used in this paper: **CI, confidence interval; GI, gastrointestinal; NMS, non-motor symptoms; OR, odds ratio; PD, Parkinson's disease**

Most current article

2772-5723
https://doi.org/10.1016/j.gastha.2022.12.005

Received July 22, 2022. Accepted December 22, 2022.

Conflicts of Interest:
These authors disclose the following: AV has served as a consultant to Alexion Pharmaceuticals, Biogen, and XW Pharma. BK has received research support from AstraZeneca, Takeda, Gelesis, Medtronic, Genzyme and has served as a consultant to Shire, Takeda, and Ironwood. The remaining authors disclose no conflicts.

Funding:
The authors report no funding.

Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Data and analytic methods are presented in the article and in the Supplementary Information section. Additional data are available upon request from other researchers by contacting the corresponding author.

Reporting Guidelines:
STROBE, SAGER.