ORIGINAL ARTICLE

More than constipation – bowel symptoms in Parkinson's disease and their connection to gut microbiota

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Background and purpose: The majority of Parkinson's disease (PD) patients suffer from gastrointestinal symptoms of which constipation is considered the most prominent. Recently, in addition to constipation, a diagnosis of irritable bowel syndrome (IBS) was also found to be associated with increased PD risk. Gut microbiota alterations have been reported in IBS and recently also in PD. IBS-like bowel symptoms in PD and their possible connection to other non-motor symptoms and faecal microbiota were assessed.

Methods: This case–control study compared 74 PD patients with 75 controls without any signs of parkinsonism or potential premotor symptoms. IBS-like symptoms were assessed using the Rome III questionnaire. The non-motor symptoms were assessed using the Non-Motor Symptoms Questionnaire and Non-Motor Symptom Scale. Faecal microbiota were assessed by pyrosequencing of the V1–V3 regions of the bacterial 16S ribosomal RNA gene.

Results: Symptoms that were IBS-like were significantly more prevalent in PD patients than in controls (24.3% vs. 5.3%; $P = 0.001$). Criteria for functional constipation were met by 12.2% of PD patients and 6.7% of controls ($P = 0.072$). PD patients with IBS-like symptoms had more non-motor symptoms and a lower faecal abundance of *Prevotella* bacteria than those without IBS-like symptoms.

Conclusion: Our results indicate that PD patients may suffer from colonic dysfunction beyond pure constipation. Therefore, a more comprehensive assessment of bowel symptoms could provide valuable information. The lower abundance of *Prevotella* bacteria in PD patients with IBS-like symptoms suggests that the microbiota–gut–brain axis may be implicated in the gastrointestinal dysfunction of PD patients.

Introduction

Constipation can affect up to 70% of patients with Parkinson's disease (PD) [1]. It is also a frequent premotor symptom and is considered one of the strongest risk factors for PD [2,3]. The pathophysiological mechanisms behind constipation in PD include prolonged intestinal transit and pelvic floor dyssynergia [4,5]. Despite its high prevalence, no specific constipation questionnaire has been validated in PD patients [6].

The Rome III criteria used in this study are a standard method for assessing functional gastrointestinal disorders such as functional constipation (FC) and irritable bowel syndrome (IBS), since no biomarkers have been identified [7]. In the recently published updated Rome IV criteria, functional gastrointestinal disorders are defined as disorders of gut–brain interaction [8]. As stated by Drossman in the overview of the Rome IV criteria, 'It is a group of disorders classified by gastrointestinal symptoms related to any combination of the following: motility disturbance,

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visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing'.

A diagnosis of IBS has recently been linked to an elevated risk of PD [9]. However, a detailed assessment of IBS symptoms in PD patients vs. control subjects has not been published previously. It was hypothesized that a subgroup of constipated PD patients might actually suffer from a more complicated spectrum of bowel symptoms, equivalent to an IBS-like phenotype. Furthermore, it was speculated that the presence of IBS-like symptoms in PD patients (IBS+) would be associated with the presence of other non-motor symptoms and with alterations of gut microbiota.

Methods

The ethics committee of the Hospital District of Helsinki and Uusimaa approved the study, and all participants gave informed consent.

Study subjects

This case–control study compared patients with a diagnosis of PD according to the Queen Square Brain Bank criteria with control subjects frequency matched for sex and age (±5 years) without any signs of parkinsonism or potential premotor symptoms. Subjects were initially recruited to compare their faecal microbiota [10]. The detailed exclusion criteria are presented in Table S1. Seventy-four patients and 75 control subjects were included in the final analysis. Five of these were not included in the microbiota study because of delayed sample acquisition (one patient) or because stool samples yielded <4500 high-quality sequences.

Clinical data

Parkinsonian symptoms were measured using the Unified Parkinson's Disease Rating Scale (UPDRS) and the modified Hoehn and Yahr scale. Overall prevalence and severity of non-motor symptoms were assessed using the Non-Motor Symptoms Questionnaire (NMSQuest) [11] and Non-Motor Symptom Scale (NMSS) [12]. Bowel symptoms were assessed using the Rome III questionnaire [7]. IBS+ was defined as abdominal pain or discomfort – experienced at least 2 days a week – that was associated with two or more of the following features: improvement with defaecation, onset associated with a change in frequency or form of stools.

Functional constipation criteria included two or more of the following features during at least 25% of defaecations for 3 months: straining, lumpy or hard stools, sensation of incomplete evacuation, manual manoeuvres to facilitate, or fewer than three defaecations per week. Additional criteria were symptom onset at least 6 months prior to diagnosis, loose stools rarely present without the use of laxatives, and that criteria for IBS+ symptoms were not fulfilled [7].

Microbiota analysis

The community structure of the faecal microbiota of the study subjects was assessed using pyrosequenced 16S rRNA gene V1–V3 amplicon data. The details of the DNA extraction, amplification and sequencing methods have been published previously [10].

Statistical analysis

The statistical analyses, except for microbiome analysis, were performed using IBM SPSS Statistics version 22.0.0 (IBM Corp., Armonk, NY, USA). Unpaired t tests were used to analyse group differences of clinical parameters for normally distributed variables; otherwise the Mann–Whitney U test was used. Fisher's two-sided exact test was used for differences regarding categorical variables. P values below 0.05 were considered significant. Odds ratios and 95% confidence intervals (CI) were calculated for gastrointestinal disorders and individual gastrointestinal symptoms. Uncorrected P values were used for identification of potential confounders with a threshold at $P < 0.2$. Logistic regression was used to evaluate the effect of potential confounders on the connection between PD and IBS-like symptoms.

A non-parametric Mann–Whitney U test was used to determine whether IBS+ patients also had more other non-motor symptoms than PD patients without IBS-like symptoms (IBS–). For this analysis items related to lower gastrointestinal tract symptoms that are covered by the Rome III IBS module were omitted (item 5, constipation or straining during defaecation, and 7, incomplete defaecation in NMSQuest, and item 21, constipation in NMSS). The Benjamini–Hochberg correction for multiple comparisons was used for individual Rome III items, NMSQuest items and NMSS domains.

Microbiome data were managed in R using the phyloseq package [13], and the differential abundances of bacterial taxa were tested with the DESeq2 package [14], which is based on negative binomial generalized linear models. The comparisons were run only for taxa that were present in at least seven samples. False discovery rate corrected P values below 0.05 were considered significant.

Results

For most of the studied clinical variables, there were no statistically significant differences between patient and control groups (Table 1). Atrial fibrillation, transient ischaemic attack or ischaemic stroke, and use of warfarin and statins were significantly more common in controls. All but two PD patients were using antiparkinsonian medication, and 61 (82.4%) were using more than one. One PD patient reported regular use of laxatives and another occasional use of antidiarrhoeal medication.

Bowel symptoms

Symptoms that were IBS-like were significantly more common in PD patients than controls (Table 2). Table S2 shows the distribution of different IBS subtypes. All symptoms associated with FC were more common in PD patients than controls (Table 2). After multiple comparison correction, the differences remained significant for all items except for 'need to help stool passage with hand'. Of the 35 PD patients who had constipation according to the NMSQuest, 17.1% fulfilled the criteria for FC and 42.9% for IBS indicating a broader spectrum of symptoms than pure constipation. Moreover, 14.9% of PD patients had loose, mushy or watery stools at least often (i.e. about 50% of the time) and 58.1% at least sometimes (i.e. about 25% of the time), which was about the same prevalence as in controls (16.0% and 57.3%, $P = 1.000$).

To estimate the effect of potential confounders on the association between PD disease status (group) and IBS-like symptoms, a binary logistic regression was performed. Covariates were selected based on differential

Table 1 Selected demographic and clinical data of subjects, including all parameters with significantly different distributions between groups

	PD ($n = 74$)	Control ($n = 75$)	P
Demographics			
Female subjects	48.6%	48.0%	1.000
Age (years, mean ± SD)	65.2 ± 5.5	64.5 ± 6.8	0.483
BMI (kg/m^2 median, IQR)	26.3 [23.8–29.3]	26.2 [23.7–28.1]	0.795
Clinical features			
UPDRS III total (mean ± SD)	31.27 ± 9.027	NA	NA
Hoehn and Yahr stage			
1	5.4%	NA	NA
1.5	2.7%	NA	NA
2	31.1%	NA	NA
2.5	39.2%	NA	NA
3	21.6%	NA	NA
Jankovic motor phenotype			
Mixed	13.5%	NA	NA
PIGD	55.4%	NA	NA
Tremor dominant	31.1%	NA	NA
Comorbidities			
Cholecystectomy	12.2%	4.0%	0.078
Atrial fibrillation	4.1%	17.3%	**0.015**
Hypercholesterolaemia	68.3%	84.4%	0.055
TIA or ischaemic stroke	6.8%	36.0%	**< 0.001**
Hyperthyroidism (resolved)	4.1%	0.0%	0.120
Medication			
Levodopa	54.1%	0.0%	**< 0.001**
COMT inhibitor	14.9%	0.0%	**< 0.001**
Dopamine agonist	78.4%	0.0%	**< 0.001**
MAO-B inhibitor	71.6%	0.0%	**< 0.001**
Anticholinergic	9.5%	0.0%	**0.006**
Amantadine	2.7%	0.0%	0.245
Warfarin	1.4%	14.7%	**0.005**
ACE inhibitor or ATR antagonist	29.7%	45.3%	0.063
Statin	20.3%	54.7%	**< 0.001**
SSRI	8.1%	2.7%	0.166
Probiotics	28.4%	22.7%	0.457

ACE, angiotensin converting enzyme; ATR, angiotensin receptor; BMI, body mass index; COMT, catechol-*O*-methyltransferase; IQR, interquartile range; MAO-B, monoamine oxidase B; NA, not applicable; PD, Parkinson's disease; PIGD, postural instability and gait difficulty; SSRI, selective serotonin re-uptake inhibitor; TIA, transient ischaemic attack; UPDRS III, Unified Parkinson's Disease Rating Scale, part 3. Significant values are indicated in bold ($P < 0.05$).

Table 2 Prevalence of IBS, FC and related symptoms in PD patients and controls

	PD (n = 74)	Control (n = 75)	OR (95% CI)	P (uncorrected)	P (corrected)
Rome III					
IBS	24.3%	5.3%	5.71 (1.83–17.82)	**0.001**	
FC	12.2%	4.0%	3.32 (0.86–12.81)	0.078	
Bowel symptoms					
Abdominal pain or discomfort[a]	29.7%	10.7%	3.54 (1.46–8.60)	**0.004**	**0.038**
Infrequent bowel movements[b]	44.6%	17.3%	3.84 (1.81–8.15)	**<0.001**	**0.006**
Hard or lumpy stools[b]	78.4%	54.7%	3.01 (1.47–6.15)	**0.003**	**0.031**
Straining during defaecation[b]	86.5%	64.0%	3.60 (1.59–8.14)	**0.002**	**0.029**
Incomplete emptying[b]	70.3%	37.3%	3.97 (2.00–7.86)	**<0.001**	**0.013**
Sensation of blocked stool[b]	36.5%	10.7%	4.81 (2.01–11.51)	**<0.001**	**0.019**
Need to help stool passage with hand[b]	21.6%	9.3%	2.68 (1.03–6.96)	**0.043**	**0.044**
Loose, mushy or watery stools[b]	58.1%	57.3%	1.03 (0.54–1.98)	1.000	NS
NMSQuest					
Constipation	47.3%	8.0%	10.32 (3.99–26.71)	**< 0.001**	
Incomplete defaecation	45.9%	10.7%	7.12 (3.00–16.89)	**< 0.001**	
NMSS					
Constipation	47.3%	6.7%	12.56 (4.55–34.69)	**< 0.001**	

CI, confidence interval; FC, functional constipation; IBS, irritable bowel syndrome; NMSQuest, Non-Motor Symptoms Questionnaire; NMSS, Non-Motor Symptom Scale; NS, not significant; OR, odds ratio; PD, Parkinson's disease; P (corrected), significance threshold corrected by Benjamini–Hochberg. [a]At least 2–3 days per month; [b]at least sometimes (i.e. about 25% of the time). Significant values are indicated in bold ($P < 0.05$).

prevalence in PD and control groups (Table 1). Due to the comparably small sample size the model including all covariates was unstable. Therefore, each covariate was studied separately in combination with the study group variable. In all models, the effect of group (PD versus controls) remained significant (Table S3). In the final model with resolved hyperthyroidism and hypercholesterolaemia as potential confounders, PD patients were 6.86 (95% CI 1.80–26.06) times more likely to have IBS+ than controls.

There was no difference in time from motor or non-motor symptom onset between IBS+ and IBS− patients (Table 3). There were no statistically significant differences in use of antiparkinsonian medication between IBS+ and IBS− patients.

The faecal microbiota

The abundances of bacterial taxa in faecal samples were compared with DESeq2 on the family, genus and OTU (Operational Taxonomic Unit, a computational proxy for species) levels between IBS+ and IBS− patients. Two statistical models were used: (i) a univariate model with IBS+/− as the only covariate; (ii) a multivariate model including IBS status and potential confounders. As confounders, the variables that had differences in prevalence between IBS+ and IBS− PD patients were selected (Table 3: hypothyroidism, lactose intolerance, gender, body mass index, dopamine agonist use and Jankovic tremor score). The univariate model suggested a significantly lower abundance of the genus *Prevotella* and the family Prevotellaceae in IBS+ compared to IBS− patients (Table 4). The multivariate model confirmed these two taxa, as well as one OTU that represents the genus *Bacteroides*, which was also less abundant in IBS+ PD patients (Table 4, Fig. 1). None of the potential confounders showed a statistically significant association with the taxa of interest (adjusted P value >0.1 for all confounders and all three taxa).

A similar comparison including both controls and PD patients was not done, since there were only four control subjects with IBS.

Symptoms that were IBS-like and other non-motor symptoms

In PD patients, IBS+ was associated with more reported non-motor symptoms (Table 5). After multiple comparison correction for individual symptoms, only the difference in the presence of unexplained pain remained statistically significant (IBS+, 55.6%; IBS−, 10.7%; $P < 0.001$). Also total non-motor symptoms burden, as measured by NMSS, seemed higher in IBS+ patients [41.5 (27.3–83.5) vs. 33.5 (20.8–50.8), $P = 0.079$], although the difference was not statistically significant.

Discussion

To our knowledge, this is the first time increased prevalence of IBS-like symptoms and related microbiome alterations have been reported in PD patients. According to Rome III criteria, 36.5% of

Table 3 Selected demographic data of PD patients, including all parameters with significantly different distributions between groups

PD patients	IBS+ (n = 18)	IBS− (n = 56)	P
Demographics			
Female subjects	77.8%	39.3%	**0.006**
Age (years, mean ± SD)	66.3 ± 5.2	64.9 ± 5.6	0.342
BMI (kg/m^2 median, IQR)	25.3 (22.9–26.6)	26.8 (24.1–29.8)	0.062
Clinical features			
Time from NMS onset (years, median, IQR)	8.50 (4.75–13.25)	6.00 (2.00–10.00)	0.244
Time from motor symptom onset (years, median, IQR)	6.00 (2.75–10.00)	5.00 (3.00–8.50)	0.484
UPDRS III (sum, mean ± SD)	29.11 ± 8.29	31.96 ± 9.22	0.246
Jankovic PIGD score (median, IQR)	0.40 (0.40–0.65)	0.60 (0.40–0.80)	0.361
Jankovic tremor score (median, IQR)	0.31 (0.22–0.41)	0.38 (0.25–0.63)	**0.046**
Hoehn and Yahr (median, IQR)	2.25 (2.00–2.50)	2.50 (2.00–2.50)	0.285
Comorbidities			
Lactose intolerance	33.3%	5.4%	**0.005**
Hypothyroidism (controlled)	33.3%	3.6%	**0.002**
Medication			
Levodopa	72.2%	48.2%	0.104
COMT	16.7%	14.3%	1.000
Dopamine agonist	61.1%	83.9%	0.053
MAO-B inhibitor	66.7%	73.2%	0.764
Anticholinergic	0.0%	12.5%	0.184
Amantadine	0.0%	3.6%	1.000
Thyroxine	33.3%	3.6%	**0.002**

BMI, body mass index; COMT, catechol-*O*-methyltransferase; IBS+, PD patients with irritable bowel syndrome; IBS−, PD patients without irritable bowel syndrome; IQR, interquartile range; MAO-B, monoamine oxidase B; NMS, non-motor symptoms; PD, Parkinson's disease; PIGD, postural instability and gait difficulty; UPDRS III, Unified Parkinson's Disease Rating Scale, part 3. Bold indicates significant values ($P < 0.05$).

Table 4 Results of DESeq2 comparisons for differential abundance of faecal microbiota in PD patients, only showing taxa with an adjusted P value < 0.05

Family	Genus	OTU	Base mean	$\log_2$(fold change)	$\log_2$(fold change) SE	P value for IBS	Adjusted P value for IBS
Model 1: taxon ~ IBS (no/yes)							
Prevotellaceae	*Prevotella*	(all)	105.70	−5.821	0.968	1.80E-09	2.28E-07
Prevotellaceae	(all)	(all)	214.95	−3.288	0.857	1.25E-04	6.62E-03
Model 2: taxon ~ hypothyroidism + lactose intolerance + gender + BMI + meds dopamine agonist + tremor score Jankovic + IBS (no/yes)							
Bacteroidaceae	*Bacteroides*	Otu0013	109.58	−3.929	0.944	3.16E-05	2.44E-02
Prevotellaceae	*Prevotella*	(all)	136.48	−5.674	1.141	6.64E-07	8.43E-05
Prevotellaceae	(all)	(all)	214.95	−3.651	1.021	3.50E-04	1.85E-02

BMI, body mass index; IBS, irritable bowel syndrome; OTU, operational taxonomic unit.

PD patients fulfilled the criteria for IBS or FC, but in this group IBS+ was actually more prevalent than FC. A recent Japanese study reported IBS criteria to be fulfilled in 17.0% and FC in 27.1% of PD patients [15]. Moreover, 58.1% of PD patients in our study had symptoms of diarrhoea.

The prevalence of constipation was higher when assessed both with the NMSQuest or the NMSS than with the Rome III criteria. However, comparisons between these questionnaires are problematic. First, the NMSS was designed to assess the 'burden' (i.e. frequency and severity) rather than the prevalence of non-motor symptoms. Secondly, the sensitivity to experienced symptoms varies. In the NMSS, those who have experienced symptoms at least 'rarely' are considered positive, whereas in the Rome III questionnaire symptoms that occur rarely are considered negative. In contrast, the NMSQuest has only yes-or-no options, giving no information about frequency of the symptoms.

Parkinson's disease patients with IBS-like symptoms (IBS+) reported more non-motor symptoms, in particular pain and symptoms of dysautonomia. Our findings suggest that IBS-like symptoms could be a manifestation of a more generalized dysautonomic phenotype of PD [16].

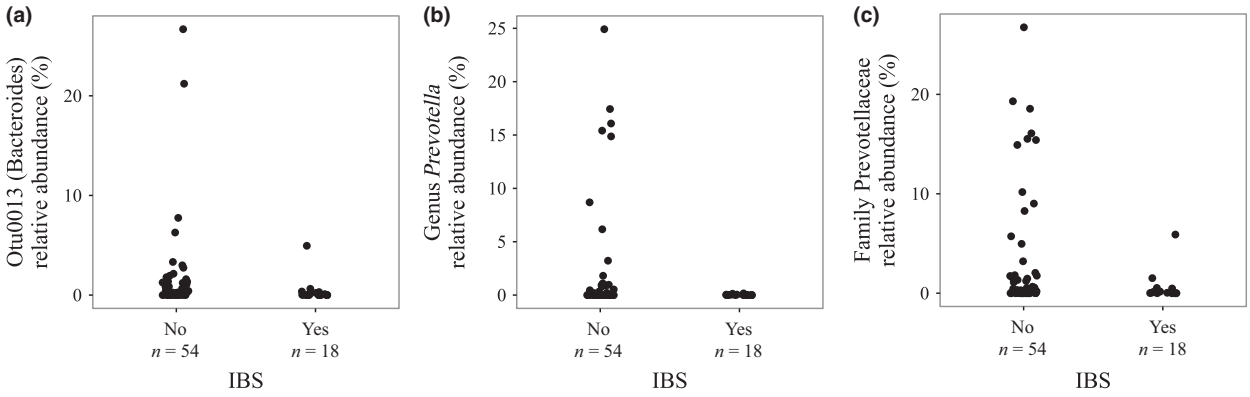

Figure 1 Bacteria with significant differences in relative abundance between PD patients with or without IBS-like symptoms.

Parkinson's disease, IBS-like symptoms and microbiota

Dysregulation of the gut–brain axis and alterations in the composition of intestinal microbiota have been previously linked to IBS pathogenesis and symptoms [17]. Several studies have reported a higher relative abundance of Firmicutes and reduction in the relative abundance of Bacteroidetes and Bifidobacteria in IBS patients [18,19]. The results for the abundance of *Prevotella* have not been consistent [18,20]. However, since our patients suffer from PD and multiple comorbidities that can possibly affect gut microbiota, comparisons with previous studies contrasting IBS patients and healthy controls are challenging.

Changes in the gut microbiota might lead to low-grade inflammation and increased permeability of the gut mucosa previously linked to IBS [21,22]. Gut mucosal changes have also been reported in PD and it has been speculated whether this could initiate α-synuclein associated neurodegeneration in the enteric nervous system that subsequently spreads to the central nervous system as initially proposed by Braak [23,24].

Previous studies in this cohort suggested alterations of the intestinal microbiota in PD patients [10]. In particular, the abundance of the family Prevotellaceae was lower in the faeces of PD patients compared with controls. These changes in microbiota were not explained by IBS. In addition, the relative abundance of Enterobacteriaceae was positively associated with the severity of postural instability and gait difficulty, i.e. the motor phenotype. Interestingly, the results from the present study suggest that gut microbiota are also associated with the non-motor phenotype of PD [16]. In particular, Prevotellaceae emerged as a key species related to PD, and now also to PD-associated IBS-like symptoms in our cohort. Since IBS has been recently proposed as a risk factor for PD [9], these observations warrant further studies of gut microbiota in the premotor stage of PD to assess whether microbiota could serve as a biomarker or a therapeutic target.

Subject characteristics and limitations

Strict inclusion and exclusion criteria and verification procedures for the PD diagnosis were used. Importantly, previously diagnosed active IBS was an exclusion criterion, as the study population was originally recruited to analyse faecal microbiota in relation to PD. Furthermore, most other gastrointestinal disorders (e.g. inflammatory bowel diseases and coeliac disease) that can cause IBS-like symptoms were excluded from this study (Table S1). It is acknowledged that for functional gastrointestinal disorder diagnosis, the presence of obvious anatomical or physiological abnormalities should be excluded [25] and that autonomic dysfunction and other neurodegeneration associated with PD could be characterized as such abnormalities. However, our goal here was to assess the complexity of bowel symptoms experienced by PD patients rather than to set a definitive diagnosis.

The high prevalence of IBS-like symptoms in our cohort therefore suggests that the Rome questionnaire would add valuable information about bowel symptoms in PD patients.

It should also be considered that controls with potential premotor symptoms of PD were excluded. This included the accumulation of non-motor symptoms as measured by the NMSQuest (Table S1). This could have caused the prevalence of IBS-like symptoms in our control group to be less than the prevalence in the general population. However, the prevalence in our control group (5.3%) is close to what has been previously reported from the Finnish

Table 5 Non-motor symptoms of PD patients with or without IBS-like symptoms

PD patients	IBS+ (n = 18)	IBS− (n = 56)	P (uncorrected)	P (corrected)
NMSQuest[a] (median, IQR)	11 (7.0–13.3)	7 (4.0–10.0)	**0.004**	
Gastrointestinal complaints				
Dribbling saliva	22.2%	35.7%	0.390	NS
Taste or smelling	50.0%	64.3%	0.406	NS
Swallowing	27.8%	21.4%	0.748	NS
Nausea or vomiting	11.1%	1.8%	0.145	NS
Bowel incontinence	16.7%	5.4%	0.150	NS
Cardiovascular abnormalities				
Feeling light headed	66.7%	37.5%	0.055	NS
Falling	5.6%	3.6%	1.000	NS
Urinary problems				
Urgency	88.9%	64.3%	0.074	NS
Nocturia	94.4%	62.5%	**0.009**	NS
Cognitive impairment/apathy				
Memory problems	38.9%	26.8%	0.380	NS
Loss of interest	33.3%	14.3%	0.090	NS
Concentrating	38.9%	32.1%	0.775	NS
Anxiety/depression				
Feeling sad	50.0%	37.5%	0.413	NS
Anxiety	16.7%	7.1%	0.350	NS
Hallucination/delusions				
Hallucinations	16.7%	5.4%	0.150	NS
Delusions	0.0%	1.8%	1.000	NS
Sexual disturbances				
Change in sex drive	72.2%	37.5%	**0.014**	NS
Sex difficulty	55.6%	26.8%	**0.043**	NS
Sleep				
Daytime sleepiness	11.1%	25.0%	0.327	NS
Insomnia	61.1%	44.6%	0.283	NS
Intense vivid dreams	27.8%	19.6%	0.517	NS
Acting out during dreams	33.3%	17.9%	0.195	NS
Restless legs	55.6%	25.0%	**0.022**	NS
Miscellaneous/others				
Unexplained pains	55.6%	10.7%	**< 0.001**	**0.0017**
Change in weight	27.8%	12.5%	0.150	NS
Swelling of legs	50.0%	39.3%	0.584	NS
Excessive sweating	33.3%	26.8%	0.764	NS
Diplopia	16.7%	8.9%	0.393	NS
NMSS[b] (score, median, IQR)	41.5 (27.3–83.5)	33.5 (20.8–50.8)	0.079	
NMSS domains (median, IQR)				
Cardiovascular	3.0 (0.8–4.5)	0.0 (0.0–2.0)	**0.006**	NS
Fatigue and sleep	11.5 (5.5–16.0)	6.5 (3.0–12.0)	0.086	NS
Mood and cognition	2.0 (0.0–8.0)	1.0 (0.0–3.0)	0.309	NS
Perceptual problems	0.0 (0.0–4.3)	0.0 (0.0–0.0)	**0.040**	NS
Attention and memory	2.5 (1.8–6.5)	2.0 (0.0–4.8)	0.119	NS
Gastrointestinal tract	5.0 (2.5–9.0)	2.0 (0.0–4.8)	**0.009**	NS
Urinary	5.0 (3.0–18.5)	5.5 (3.0–10.0)	0.404	NS
Sexual function	2.0 (0.0–9.0)	1.0 (0.0–7.0)	0.433	NS
Miscellaneous	8.0 (5.5–18.5)	8.0 (4.0–12.8)	0.354	NS

IBS, irritable bowel syndrome; IBS+, PD patients with IBS-like symptoms; IBS−, PD patients without IBS-like symptoms; IQR, interquartile range; NMSQuest, Non-Motor Symptoms Questionnaire; NMSS, Non-Motor Symptom Scale; PD, Parkinson's disease; P (corrected), significance threshold corrected by Benjamini–Hochberg. [a]Items 5 (constipation) and 7 (incomplete defaecation) excluded; [b]item 21 (constipation) excluded. Bold indicates significant values ($P < 0.05$).

population (5.1%), although this study used different criteria for IBS [26].

Finally, medications and comorbidities can modulate gastrointestinal symptoms and microbiota [10]. Using a liberal threshold of $P < 0.1$ for identifying potential confounders, only lactose intolerance and the use of thyroxin and dopamine agonist were differentially distributed between the groups. Thus they

were added as confounders in the model. It is believed that this adequately controls for the effect of dopamine agonists. However, since in the IBS− group only two subjects were using thyroxin medication, and three reported lactose intolerance, a confounding effect on our microbiota findings cannot be completely excluded.

Conclusions

Our findings suggest that PD patients may suffer from colonic dysfunction beyond pure constipation as part of a dysautonomic non-motor phenotype. This could also be associated with a lowered pain threshold and dysfunction of the gut−brain axis with possible implication of gut microbiota. A more comprehensive assessment of bowel symptoms using the Rome III (or the newest Rome IV) questionnaire could provide a basis for better understanding of the gastrointestinal dysfunction in PD. If the connection between PD, IBS and microbiota is confirmed by further studies, PD research and management could profit from the accumulating evidence on the pathophysiology and treatment of IBS.

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Disclosure of conflicts of interest

F.S., V.T.E.A., P.A.B.P., L.P. and P.A. are listed as inventors on patent application WO2015/181449A1. F.S. is founder and CEO of NeuroInnovation Oy. The authors report no other conflicts of interest relative to the research covered in this paper.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Exclusion criteria.
Table S2. Prevalence of IBS subtypes in PD patients and controls.
Table S3. Binary logistic regression for the potential confounders on the association between PD disease status (group) and IBS.

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