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Colonic transit, high-resolution anorectal manometry and MRI defecography study of constipation in Parkinson's disease

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ABSTRACT

Introduction: Despite clinical relevance and potential role on the disease pathogenesis, underlying mechanisms of constipation in Parkinson's disease (PD) remain poorly understood. A systematic assessment using complementary physiological investigations was performed to elucidate constipation pathophysiology in order to improve its symptomatic management.

Methods: PD patients with constipation were evaluated with clinical questionnaires, colonic transit, high-resolution anorectal manometry and MRI defecography. Results were compared and correlated with clinical features.

Results: A total of 42 patients (69% male; age 68 ± 8 years; disease duration 10.5 ± 6.1 years) were included, of whom 33 (78.6%) had objective constipation defined by < 3 bowel movements per week or straining. Severity of constipation measured by self-administered questionnaires correlated with disease severity, burden of motor and non-motor symptoms but not with age, disease duration or Parkinson's medications. Colonic transit and anorectal function (high-resolution anorectal manometry and/or MRI defecography) was assessed in 15 patients. A combination of both delayed colonic transit and anorectal dysfunction was the pattern most commonly found (60% of patients) and overall anorectal dysfunction was more prevalent than isolated slow transit constipation. Physiological findings were heterogeneous including reduced colonic motility, rectal hyposensitivity, defecatory dyssynergia and poor motor rectal function.

Conclusion: Subjective constipation in PD is poorly correlated with commonly used definition, assessment questionnaires and physiological results. Multiple complex overlapping pathophysiological mechanisms are responsible including slow transit and anorectal dysfunction. Complementary investigations to assess colonic transit and anorectal function are required in those with refractory symptoms for a systematic assessment and appropriate symptomatic management.

1. Introduction

Accumulating evidence implicates early gastrointestinal (GI) dysfunction in Parkinson's disease (PD) contributing to the clinical burden of non-motor features [1]. Constipation is the most common GI symptom in PD with an estimated prevalence of approximately 50% [2]. Constipation is a subjectively perceived symptom including manifestations such as hard stools, reduced bowel movements, bloating, abdominal pain and straining during defecation, although several objective criteria have been developed to help its clinical assessment. From a pathophysiological perspective, constipation can be divided in slow transit constipation and defecatory dysfunction.

Despite its clinical relevance, no objective criteria have been developed to evaluate constipation specifically in PD and multiple terms have been used in previous literature without a consensus definition [2]. The pathophysiology of constipation in PD remains poorly

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understood and this carries important clinical implications as symptomatic management of slow transit and defecatory dysfunction differ significantly. Previous literature prevent any firm conclusions due to limitations in study design and heterogeneity of results [1,2]. Firstly, a wide range of definitions of constipation has been used in PD and consensus criteria for the assessment of functional chronic constipation in the general population have not been properly validated in PD research. Secondly, most of the previous studies reported results of investigations in isolation, without other additional complementary tests to allow a systematic evaluation of the symptoms [3–6]. These investigations are of little clinical utility when individually performed because of the difficulties in interpreting the results given the overlap between health and disease, the lack of correlation between a single physiological abnormality and symptoms, and the commonly multifactorial cause of the problem [7,8]. Additionally, most of these studies were performed a few decades ago with conventional historical diagnostic techniques and, with a few exceptions reporting results using high-resolution ARM [5,9], more recent studies have not incorporated technological advances.

Here we report the results of a systematic assessment of patients with PD and subjective constipation. Diagnostic criteria and severity of symptoms was evaluated using validated questionnaires for the assessment of chronic constipation commonly used in clinical practice and compared to the patient perception of the symptoms in order to assess their accuracy. Colonic transit, high-resolution anorectal manometry (ARM) and MRI defecography were performed in a subgroup of patients. Results of these investigations are reported individually and also interpreted in conjunction in order to provide a better understanding of the pathophysiological correlation of constipation in patients with PD. Finally, based on these results, recommendations for the clinical evaluation of constipation and the use of these investigations in patients with PD are provided.

2. Methods

2.1. Subjects and study design

Participants with a diagnosis of PD based on the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria [10] and subjective complaints of constipation were prospectively recruited from the specialist clinic at the National Hospital for Neurology, London, between June 2016 and February 2018. Participants were recruited based on their subjective perception of their symptoms in order to capture the wide range of manifestations described under the term constipation and to allow a comparison with objective definition commonly used in clinical practice. Patients with the following features were excluded: secondary or atypical parkinsonism, pregnancy, major colonic or pelvic floor surgery, organic colonic disease (i.e. inflammatory bowel disease, severe diverticulosis,..), systemic connective tissue disorders (scleroderma), active psychiatric disorder or chronic regular opioid use (> 1 take per day). All patients provided informed written consent and the study was approved by the Research Ethics Committee.

Only patients on stable medication were included in the study (no drug changes within two months). Participants were assessed while on their regular medications, including treatment with anticholinergics, although laxatives were suspended prior to colonic transit. Medications were not discontinued to facilitate participant recruitment, minimise patient disturbance and evaluate constipation in real-life clinical settings, where these medications are commonly used for symptomatic management of PD. Clinical and demographic data were recorded. Severity of PD related symptoms was assessed using the Hoehn and Yahr scale (HY) for disease stage, the part III of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) for motor symptoms and the non-motor symptom questionnaire (NMSQ).

2.2. Constipation questionnaires

The score for questions related to GI symptoms from the NMSQ (questions 5–7) were recorded separately. To specifically evaluate the extent and severity of constipation patients completed self-administered questionnaires namely the Patient Assessment of Constipation Symptoms questionnaire (PACSYM) and the Neurogenic Bowel Dysfunction score (NBD). PACSYM comprises 12 questions (divided in abdominal, rectal and stool domains) using a five-point scale from absent to very severe and is validated and widely used in patients with chronic idiopathic constipation [11,12]. NBD score is a symptom-based questionnaire (higher scores indicating more severe symptoms) developed and validated to assess colorectal dysfunction in patients with spinal cord injury including symptoms of constipation and faecal incontinence, and a modified version has been previously used in PD patients [13].

2.3. Physiological investigations

A subgroup of consenting patients underwent additional investigations interpreted blinded to the severity of symptoms.

2.3.1. Colonic transit

Colon transit was evaluated using radiopaque markers according to the standard previously described technique [14]. Three sets of radiologically distinct markers were taken at 24 h intervals and an abdominal X-ray taken 120 h after ingestion of the first set. Retention of more than the normal range for any one of the three sets of markers (< 3 of day 1 markers, < 5 of day 2 markers and < 11 of day 3 markers) was regarded as reflecting slow whole gut transit.

2.3.2. High-resolution anorectal manometry

ARM was undertaken using a custom 16 channel 4.4 mm diameter water perfused high resolution manometry catheter. The intra-anal array consisted of 13 of the 16 channels, starting at 5 mm from the anal verge and at 5 mm intervals extending to 6.5 cm from the anal verge. The proximal channels were positioned posteriorly to optimally measure the action of puborectalis. There were two further rectal channels either side of the balloon, with the final channel 15 cm distal to the anal verge measuring atmospheric pressure. Normal values for resting and incremental squeeze pressures were based on previously published data [15]. Evacuatory measurements were made during attempted balloon expulsion with the catheter clamped in situ.

2.3.3. MRI defecography

MRI defecography was performed using closed 1.5 T magnet with the patient in the left lateral supine position [16]. Patients are given a glycerine suppository 30 min prior to the procedure to empty the rectum of faecal content and 120 ml of standard ultrasound gel was introduced into the rectum via bladder syringe. Sagittal, axial and coronal T2 weighted images were performed during maximum strain and maximum contraction. A video recording was taken through the mid sagittal plane during evacuation of the rectal jelly. MRI evidence of failure of relaxation or descent of puborectalis during attempted evacuation on at least two attempts was defined as “MRI dyssynergia”; evidence of inability to void the contrast gel was defined as “MRI evacuation failure”.

2.4. Statistical analysis

Comparisons between groups were performed using chi square test for categorical variables, and *t*-test for continuous variables as appropriate. Association between variables were evaluated using Pearson correlation coefficient and Spearman rank correlation coefficient as indicated. Statistical significance was set at $p < 0.05$ and Stata 12 (StataCorp, TX) software package was used for statistical analysis.

Table 1
Demographic, clinical features and results of investigations.

	Total n = 42	CTr n = 15	ARM n = 20	MRI defecography n = 9
Age	68 ± 8	67 ± 7	67 ± 8	69 ± 7
Gender (male)	29 (69)	12 (80)	16 (80)	7 (78)
Disease duration (y)	10.5 ± 6.1	8.9 ± 5.3	9.3 ± 5.6	7.9 ± 4.0
Excellent Ldopa response	37 (88.1)	13 (86.7)	18 (90.0)	8 (77.8)
Ldopa equivalent dose (mg)	770.38 ± 429.88	629.13 ± 388.01	633.85 ± 378.39	619.8 ± 290.5
MDS-UPDRS III	27 ± 18	21 ± 14	25 ± 16	24 ± 17
HY stage				
1	4 (9.5)	2 (13.3)	3 (15.0)	1 (11.1)
2	29 (69.1)	11 (73.3)	13 (65.0)	6 (66.7)
3	5 (11.9)	1 (6.7)	2 (10.0)	1 (11.1)
4	2 (4.8)	0 (0.0)	1 (5.0)	0 (0.0)
5	2 (4.8)	1 (6.7)	1 (5.0)	1 (11.1)
NMSQ	13 ± 5	12 ± 5	12 ± 4	13 ± 6
Constipation definition*	33 (78.6)	12 (80.0)	16 (80.0)	7 (77.8)
PACSYM	12.2 ± 8.0	14.1 ± 9.1	14.8 ± 9.7	17.1 ± 9.9
NBD	6.6 ± 4.8	5.8 ± 4.6	6.7 ± 5.1	7.7 ± 5.0
Laxatives	20 (47.6)	8 (53.3)	12 (60.0)	6 (66.7)
Levodopa	38 (90.5)	13 (6.7)	17 (85.0)	9 (100.0)
Dopamine agonists	17 (40.5)	7 (46.7)	7 (35.0)	2 (22.2)
COMT	16 (38.1)	4 (26.7)	6 (30.0)	2 (22.2)
MAO-B inhibitors	19 (45.2)	6 (40.0)	8 (40.0)	3 (33.3)
Anticholinergics	9 (21.4)	2 (13.33)	9 (45.0)	2 (22.2)
Amantadine	18 (42.9)	7 (46.7)	5 (25.0)	5 (55.6)
Abnormal CTr		10 (66.7)		
ROM distribution		Right 2 (14.3)		
		Left 7 (50.0)		
		SR 5 (35.7)		
Abnormal MRI				6 (66.7)
MRI evacuation failure				6 (66.7)
MRI dyssynergia				5 (55.6)
Abnormal ARM			14 (70.0)	
Sensation			13 (65.0)	
Expulsion			1 (5.0)	
ARM sphincter			6 (30.0)	
RAI reflex			1 (5.0)	

*Constipation defined as < 3 bowel movements per week or need to strain to pass stools.
Data shown in number (%) or mean ± SD.
CTr colonic transit; RAI, rectoanal inhibitory; ROM, radiopaque marker; SR, sigmoid-rectum.

3. Results

A total of 42 patients with PD (69% male; age 68 ± 8 years; disease duration 10.5 ± 6.1 years) and subjective complaints of constipation were included in the study. Main demographic and clinical features are shown in Table 1. Most of the participants had mild-moderate disease with a MDS-UPDRS III score of 27 ± 18 and NMSQ score of 13 ± 5.

3.1. Constipation questionnaires

Despite subjective complaints of constipation, only 33 (78.6%) reported < 3 bowel movements per week or straining, a commonly used screening definition of constipation in PD [2], and only 20 (47.6%) were on regular treatment with laxatives.

The strongest correlation of severity of constipation measured by PACSYM and NBD questionnaires was found with severity of non-motor symptoms (Pearson correlation; r = 0.506; P < 0.001 and r = 0.387; P = 0.011 respectively), particularly with urinary symptoms (r = 0.352; P = 0.02) and orthostatic hypotension (r = 0.412; P = 0.007) suggesting a more widespread autonomic impairment in these patients. A positive association was also found with motor impairment, disease stage and treatment with laxatives (all P values < 0.05; see Table 2 and Fig. 1). No association was found between constipation severity and disease duration, levodopa response, treatment with anticholinergics or other PD medications (all P > 0.05; see Table 2). Treatment with anticholinergics did not show a significant association with abnormal results on colonic transit, ARM or MRI defecography (all P > 0.05).

Table 2
Comparison of constipation severity measured by PACSYM, NBD and NMSQ questionnaires with main clinical variables and investigations.

	PACSYM score	NBD score	NMSQ constipation
Age*	−0.176; 0.266	0.107; 0.500	−0.181; 0.252
Gender**	0.149	0.040	0.627
Disease duration*	0.203; 0.198	0.190; 0.229	0.120; 0.450
HY stage***	0.272; 0.081	0.367; 0.017	0.030; 0.850
MDS-UPDRS III*	0.317; 0.041	0.393; 0.010	0.061; 0.700
NMSQ*	0.506; 0.001	0.387; 0.011	0.366; 0.017
Ldopa response**	0.439	0.939	0.343
Laxatives**	0.003	0.002	0.857
Anticholinergics**	0.094	0.082	0.743
Colonic transit**	0.211	0.248	0.836
ARM**	0.981	0.941	0.865
MRI defecography**	0.016	0.010	0.105

*r Pearson correlation coefficient, P value; **t-test P value; *** Spearman rank correlation coefficient; P value.

3.2. Physiological assessment

The subgroup of patients who underwent physiological investigations did not differ significantly regarding age, gender, disease duration, severity of motor and non-motor symptoms (all P values > 0.05) although constipation severity measured by PACSYM (but not by NBD) was slightly higher on those patients having ARM and MRI defecography. Table 1 shows a summary of the results.

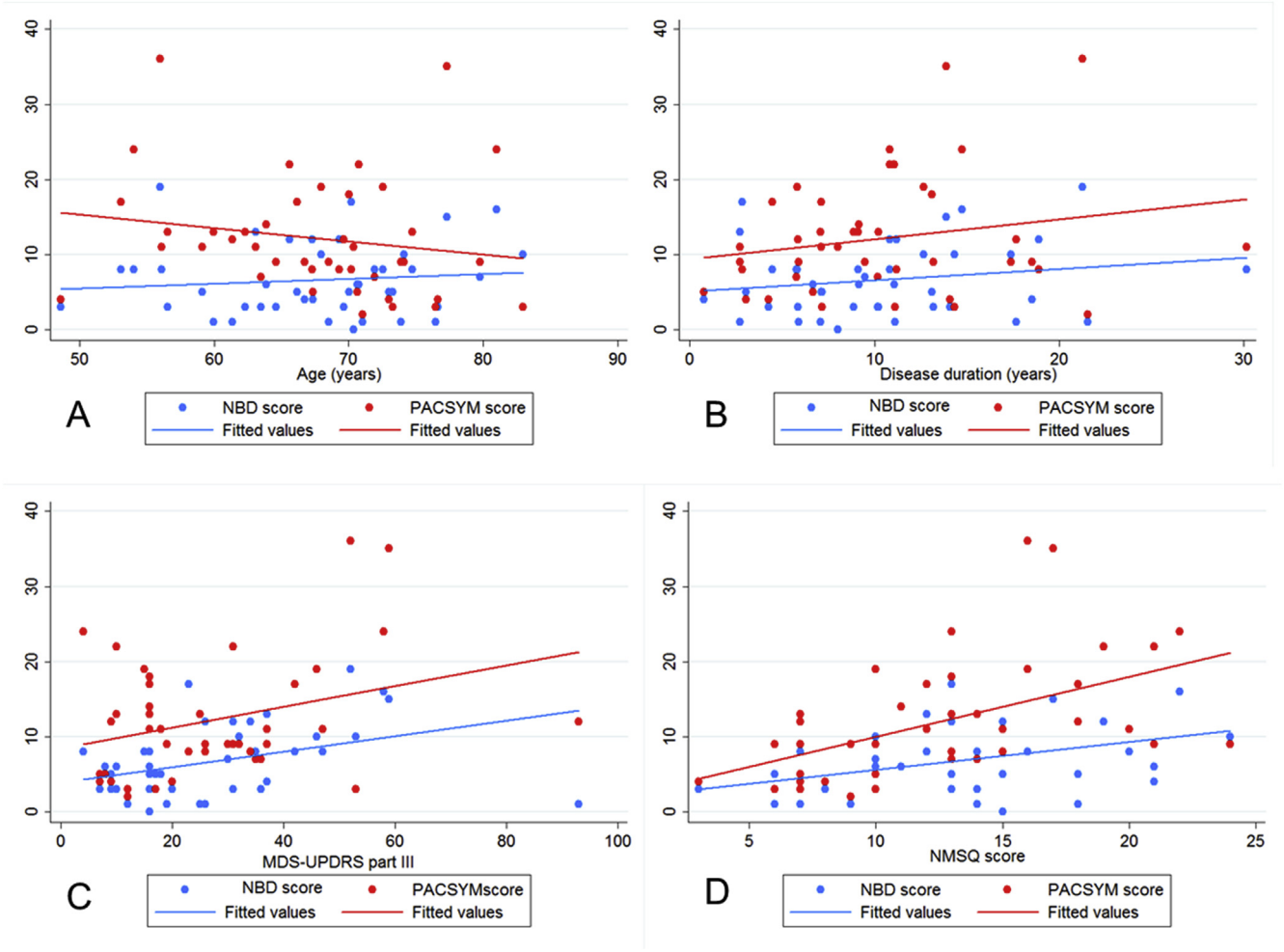

Fig. 1. Scatter plots showing correlation of constipation severity (NBD score in blue; PACSYM score in red) with age (A), disease duration (B), MDS-UPDRS part III score (C) and NMSQ score (D). See Table 2 for r correlation coefficient and P values. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.2.1. Colonic transit

Fifteen patients had colonic transit studies and slow transit was detected in 10 (66.7%). In those with < 3 depositions per week or straining, 9 out of 12 patients (75%) showed a delayed transit study, whilst this investigation was abnormal in 1 patient whose symptoms did not fulfil this definition. No clinical correlation was found between delayed transit and severity of symptoms.

3.2.2. High-resolution anorectal manometry

High-resolution ARM including balloon expulsion test was performed in 20 participants and results were abnormal in 17 (70.0%) patients, with rectal hyposensitivity (65.0%) and attenuated external anal sphincter function (30.0%) as the most common abnormal parameters. No association was found between severity of constipation and abnormal anorectal function on ARM.

Results were similar in those with an objective definition of constipation, with 68.8% (11 out of 16 patients) having an abnormal study, and reduced anal sensation being the most common underlying abnormality. Three patients with subjective constipation complaints but no objective constipation according to commonly used definition had abnormalities of anorectal function on ARM.

3.2.3. MRI defecography

Functional disorders on MRI defecography were identified in two-thirds of patients (6 out of 9), particularly findings of defecatory dyssynergia. MRI defecography was the only investigation correlated with severity of constipation measured by PACSYM (*t*-test; P = 0.016) and NBD questionnaires (*t*-test; P = 0.010) (see Table 2). When PACSYM subscores were analysed, only the stool subscore was statistically significant (*t*-test; P = 0.001) with no association to abdominal or rectal scores.

MRI defecography was abnormal in 6 out of 7 (85.7%) patients with < 3 depositions per week or straining while it did not show any abnormalities in patients with constipation symptoms not meeting these criteria.

3.3. Combined assessment of colonic transit and anorectal function

A total of 15 patients (age 67 ± 7 years; male 80%; disease duration 8.9 ± 5.3 years) underwent combined assessment of colonic transit and at least one test of anorectal function (high resolution ARM and/or MRI defecography) whilst 9 patients (age 69 ± 7 years; male 78%; disease duration 7.9 ± 4.0 years) had all three investigations. The pathophysiological interpretation of these results is shown in Fig. 2. A mixed pattern involving slow transit and anorectal dysfunction is the most common underlying pathophysiology of constipation (60.0%) and, overall, isolated anorectal dysfunction is more prevalent than isolated slow transit in PD. The analysis of the subgroup with all three investigations (n = 9) showed similar results.

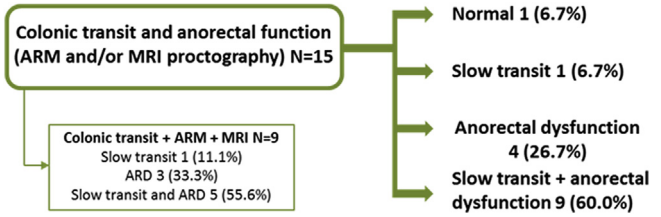

Fig. 2. Diagram showing the pathophysiological implications in patients with colonic transit and anorectal function investigations.

4. Discussion

In this prospective study we performed a systematic assessment of constipation combining colonic transit and high-resolution manometric studies, and reporting for the first time results of MRI defecography in a group of PD patients. Our findings demonstrate the pathophysiological and clinical heterogeneity of this symptom in PD, showing that multiple complex overlapping mechanisms are involved with poor correlation between subjective symptoms, current definitions used in clinical practice and objective measurements of different physiological tests.

4.1. Subjective symptoms, objective definition and severity of constipation

Despite clinical complaints of constipation only 78.6% of patients fulfilled the criteria of < 3 bowel movements per week or the need to strain to pass a stool, a definition commonly used in PD studies [2]. Comparison of subjective symptoms with physiological tests showed similar figures, with abnormal findings in two thirds of patients, presence of abnormal results in symptomatic patients not meeting the objective definition of constipation and poor correlation with symptom severity. These discrepancies reflect the lack of well-accepted and accurate clinical tools to make the diagnosis, assess the severity and the impact of constipation specifically in patients with PD. Other studies have shown similar conflicting results between subjective complaints and objective abnormalities although the latter were more commonly present than subjective symptoms [4,17]. Differences in methodologies and the lack of a comprehensive battery of investigations make any comparisons between studies challenging. Development of specific assessment scales for constipation in PD should consider its symptom-based character, incorporating the patient's perception, and should also include questions to address slow transit and defecatory dysfunction.

Severity of constipation in our study varied widely among individuals although PACSYM scores in PD patients were lower than patients with functional constipation [18]. Severity of constipation correlated with severity of the disease, including motor and non-motor symptoms in particular with other autonomic disturbances, in agreement with previous studies [13,19,20]. There was no correlation with disease duration indicating that constipation is an early symptom that can predate the diagnosis of PD for many years. Supporting this idea, constipation and manometric abnormalities have been reported in early drug-naïve patients [4] without significant differences when compared to advanced stages of the disease [5,6]. No correlations were found between severity of constipation and any of the medications used for the symptomatic treatment of PD, including anticholinergic drugs, or levodopa response suggesting a non-dopaminergic mechanism.

4.2. Physiological investigations

4.2.1. Colonic transit

Delayed colonic transit was found in 66% of our patients and has been previously reported in multiple studies in approximately 80% of patients with PD when compared to controls [17,21,22]. Although methodological differences make comparisons between studies difficult, the average transit time is estimated to be twice as long in PD patients [22,23], but not as high as in patients with idiopathic functional constipation [18]. Similar to our results, literature shows poor clinical correlation of these abnormalities [2] and delayed transit can be present in those not meeting the common definition for objective constipation [17].

4.2.2. High-resolution anorectal manometry

ARM is the best-established test for the assessment of anorectal function in clinical settings and provides a comprehensive evaluation at rest and during defecatory manoeuvres on anal sphincter function, rectal sensation, rectoanal reflex activity and pressure measurements during attempted defecation. High-resolution ARM is increasingly replacing conventional ARM as it provides a more accurate assessment, allows integrated measurements of pressures and performance of balloon expulsion test. High-resolution ARM was abnormal in 70% of our patients with rectal hyposensitivity more commonly reported although abnormal sphincter function, rectal reflex activity and balloon expulsion test were also found. Rectal hyposensitivity is likely secondary to impaired rectal afferent neurological input causing diminished perception of rectal wall distension leading to loss or attenuation of the desire to defecate and faecal impaction [24]. It is a common finding in patients with chronic functional constipation and it would appear from our study that this aetiopathogenic mechanism is also relevant in patients with PD. Previous manometric assessment in patients with PD have shown abnormalities of anorectal dysfunction in a great proportion of patients, even at early stages of the disease, with a heterogeneous pattern between studies including rectal hyposensitivity and several motor abnormalities of sphincter pressure or contractility (dyssynergia) [3,4,6,22,23,25] although only two of them incorporated high-resolution manometry [5,9]. Taken together, in addition to methodological differences and incorporation of more sensitive high-resolution equipment that may contribute to variability of results, these findings indicate that pathophysiology of defecatory dysfunction in PD is complex with multiple heterogeneous overlapping mechanisms and rectal hyposensitivity and poor evacuatory function due to dyssynergia were the most common patterns in this study.

4.2.3. MRI defecography

Defecography is a simple test involving the insertion of a stool substitute into the rectum followed by imaging at rest and during rectal evacuation that, in addition to an assessment of pelvic floor structure, allows evaluation of real-time dynamic defecatory function. We reported for the first time in PD patients the findings of defecography using MRI. All patients with abnormal results showed incomplete/delayed evacuation and findings consistent with anorectal dyssynergia (lack of relaxation of puborectalis muscle and pelvic floor descent) were found in 55%. Our results seem to be similar to previous studies on patients with functional constipation showing that MRI defecography is able to detect evacuation difficulties not only due to dyssynergic defecation, making it a useful investigation in the assessment of constipation in PD and a useful complementary diagnostic test to ARM [26].

4.2.4. Combined assessment of colonic transit and anorectal function: clinical recommendations

Our findings demonstrated that both slow transit and defecatory dysfunction contribute to constipation and overlap in the majority of patients. When analysed together, defecatory dysfunction seem more prevalent than isolated slow transit constipation. Only a very few studies have evaluated colonic transit and anorectal dysfunction simultaneously and their results agree with a predominant role for anorectal dysfunction although either manometric parameters without additional defecography were used [9,22] or studies were conducted decades ago using historical diagnostic techniques [23].

Based on the results of the current and previous studies on PD, and evidence from studies on chronic constipation in the general

population, several recommendations can be made with regards to its assessment. A full history that includes symptoms of slow transit and defecatory dysfunction should be obtained to assess the range of associated symptoms and constipation subtypes, although these may not be considered reliable indicators of underlying delayed colonic transit and anorectal dysfunction. Clinicians should always exclude red flags of an underlying malignancy, such as blood with the stools or unexplained weight loss. Investigations to elucidate underlying physiological subtypes of constipation in PD are not essential in the initial assessment, and should be reserved for those cases refractory to lifestyle modifications and first-line laxatives. These investigations are of little clinical use when individually performed and their interpretation should be made in conjunction and correlation with the symptoms, given the common multifactorial pathophysiology and the overlap between pathological and physiological parameters [7,8]. The understanding of pathophysiological mechanisms of constipation has important implications in clinical practice. Whilst slow transit is managed with diet modifications and laxatives, defecatory dysfunction is likely to be underdiagnosed and biofeedback therapy seems to be an effective therapy in around 70% of patients, earning a grade A recommendation from the American and European Neurograstroenterology and Motility Societies [1,27]. Specific studies on PD showed that some patients may also respond to apomorphine [28,29] and botulinum toxin injections [25].

The main strengths of our study are the presence of detailed clinical information on PD and constipation, the comprehensive range of investigations included to assess the multiple pathophysiological aspects of constipation in a systematic and structured manner and the inclusion of modern techniques such as high-resolution ARM or the report for the first time of MRI defecography findings in patients with PD. Our study also had some limitations. Although normal reference values and findings on patients with functional chronic constipation are available in the literature for some of these investigations, including colonic transit time [18,30], high-resolution ARM [15] and MRI defecography [31] we did not include a control group to compare our results. Our results should be interpreted with caution, particularly the findings on MRI defecography, given the relatively small sample size and the lack of previous studies using this technique on PD patients. Finally we did not discontinue any of the regular medications of the participants in order to evaluate the symptoms in real-life clinical settings, including dopaminergic medication and anticholinergics which may potentially have effects on colonic motility, although our analysis did not reveal any correlations between these medications and severity of constipation.

5. Conclusions

In summary, our study provided a comprehensive assessment with a battery of investigations that allowed a detailed pathophysiological evaluation of constipation in patients with PD. Results showed a discrepancy between patient perception of the symptoms and the definitions and severity questionnaires commonly used in clinical practice which reflects the lack of specific diagnostic tools for the assessment of this symptom in PD. Constipation in PD is likely due to a heterogeneous pattern of pathophysiological abnormalities suggesting multiple overlapping mechanisms involving both slow colonic motility and anorectal dysfunction. A battery of tests including at least one investigation assessing colonic transit and anorectal function should be included for a comprehensive pathophysiological evaluation of constipation in those with refractory constipation. These results should guide the multidisciplinary management of the symptoms with dietary modifications, laxatives and biofeedback therapy according to the underlying pathophysiological abnormalities.

Declaration of interest

None reported.

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Authors' roles and approval

EDP-F: study conception and design, acquisition of data, analysis and interpretation of data, writing of first draft.

VP: acquisition and interpretation of data, critical revision of manuscript for intellectual content.

NZ-L: acquisition and interpretation of data, critical revision of manuscript for intellectual content.

AE: study concept and design, acquisition and interpretation of the data, critical revision of manuscript for intellectual content.

TTW: study concept and design, study supervision, critical revision of manuscript for intellectual content.

All authors have read and approved the final version of the manuscript.

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