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ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Pharmacology and Therapeutics*, Dr. Tony Tham is a Consultant Gastroenterologist at Ulster Hospital, Dundonald, Belfast (Northern Ireland, United Kingdom). His publication record spans more than 80 articles and first-authorship of the "Gastrointestinal Emergencies" textbook. He has served as the Guidelines Editor for *Gut*, an International Editorial Board Member for *Gastrointestinal Endoscopy*, and Associate Editor for *Diagnostic and Therapeutic Endoscopy*. He has previously served as Chair of the British Society of Gastroenterology (BSG) Clinical Services and Standards Committee (as well as Deputy Chair and Secretary), BSG Quality Improvement lead, and Head of the School of Medicine, Northern Ireland (deanery). Currently, he is President of the Irish Society of Gastroenterology, Chair of Ireland's National Clinical Program for Gastroenterology and Hepatology, Clinical Advisory Group, and Vice Chair of the Specialist Advisory Committee for general internal medicine, Joint Royal Colleges of Physicians Training Board, United Kingdom. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of the *World Journal of Gastrointestinal Pharmacology and Therapeutics* (*WJGPT*, *World J Gastrointest Pharmacol Ther*) is to provide scholars and readers from various fields of gastrointestinal pharmacology and therapeutics with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

   WJGPT mainly publishes articles reporting research results obtained in the field of gastrointestinal pharmacology and therapeutics and covering a wide range of topics including acid-related disorders, functional gastrointestinal disorders, fundamentals of gastrointestinal pharmacology, *etc.*

INDEXING/ABSTRACTING

The *WJGPT* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Retrospective Study

Clinical features and relative factors of constipation in a cohort of Chinese patients with Parkinson's disease

Bai-Hua Sun, Tao Wang, Nian-Ying Li, Qiong Wu, Jin Qiao

Bai-Hua Sun, Nian-Ying Li, Department ofNeurology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China

Bai-Hua Sun, Department of Neurology, Xi'an Third Hospital, Xi'an 710021, Shaanxi Province, China

Tao Wang, Department ofNeurology, the Shaanxi Sengong Hospital, Xi'an 710300, Shaanxi Province, China

Qiong Wu, Jin Qiao, Department of Rehabilitation Medicine, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China

Corresponding author: Jin Qiao, MD, Professor, Department of Rehabilitation Medicine, the First Affiliated Hospital of Xi'an Jiaotong University, No. 277 West Yanta Road, Xi'an 710061, Shaanxi Province, China. qiaojn123@163.com

Abstract

BACKGROUND

Constipation as a most common non-motor symptom of Parkinson's disease (PD), has a higher prevalence compared to the general population. The etiologies of constipation in PD are diverse. In addition to physical weakness and other factors of disease, the lifestyles and eating habits are also important factors. Therefore, the prevalence and influencing factors of constipation may vary among different populations.

AIM

To determine the prevalence of constipation and analyze relative factors in a cohort of Chinese patients with PD.

METHODS

All the patients diagnosed with PD according to the movement disorders society criteria were consecutively collected by a self-developed questionnaire. Rome III diagnostic criteria were used to assess functional constipation and Wexner score was used to estimate the severity of constipation. Non-motor symptoms (NMS) were assessed with the non-motor symptoms assessment scale (NMSS). Unified Parkinson's disease Rating Scale III (UPDRS III) was used to evaluate the severity of motor symptoms. The modified Hoehn-Yahr stage was used to evaluate the severity of PD. Cognitive function was assessed using Montreal cognitive

assessment (MoCA). Depression and anxiety were rated with the Hamilton depression scale (HAMD) and the Hamilton anxiety scale (HAMA). Quality of life was assessed using the Parkinson's disease Questionnaire-39 items (PDQ-39).

RESULTS
Of 166 patients enrolled, 87 (52.41%) were accompanied with constipation, and 30 (34.48%) experienced constipation for 6.30 ± 5.06 years before motor symptoms occurred. Age, Hoehn-Yahr stage, disease duration, levodopa medication times, incidence of motor complications, the scores of UPDRS total, UPDRS III, NMSS, HAMD, HAMA, and PDQ-39 in the constipation group were higher than those in the non-constipation group ($P < 0.05$), but there was no difference in the scores of MoCA, clinical types, or medications between the two groups ($P > 0.05$). There was a higher incidence of depression in patients with constipation ($P < 0.05$), but there were no difference in the incidence of anxiety and cognitive impairment between the two groups ($P > 0.05$). As Hoehn-Yahr stages increased, the severity of constipation increased ($P < 0.05$), but not the incidence of constipation ($P > 0.05$). Pearson correlation analysis showed that constipation was moderately positively correlated with age, Hoehn-Yahr stage, and scores of NMSS, UPDRS III, UPDRS total, PDQ-39, HAMD, and HAMA ($r = 0.255, 0.172, 0.361, 0.194, 0.221, 0.237, 0.238$, and 0.207, $P < 0.05$). Logistic regression analysis showed that only NMSS score was an independent risk factor for constipation ($P < 0.001$).

CONCLUSION
Our findings confirm that constipation has a relatively high frequency in patients with PD. PD patients with constipation have a higher incidence of depression, which leads to worse quality of life.

Key Words: Parkinson's disease; Non-motor symptoms; Constipation; Clinical characteristics; Quality of life; Depression

Core Tip: This study aimed to determine the prevalence of constipation and analyze its clinical characteristics and relative risk factors in a cohort of Chinese patients with Parkinson's disease (PD). Our findings confirmed that constipation had a relatively high frequency in patients with PD. The patients with constipation had a higher incidence of depression, which led to worse quality of life.

INTRODUCTION

Parkinson's disease (PD) is a degenerative disease of the central nervous system. In addition to motor symptoms such as resting tremor, bradykinesia, myotonia, and posture imbalance, non-motor symptoms (NMS) are also very common: Olfactory dysfunction, autonomic dysfunction, mood disorders, sleep disorders, gastrointestinal symptoms, cognitive impairment, *etc*[1,2]. NMS can occur at any stage of the disease, and some even appear before the onset of motor symptoms and seriously affect quality of life, especially in later stages. In recent years, it has been considered that the brain-intestinal-microbial axis plays a significant role in pathogenesis or progression of PD. The intestinal nervous system may be the onset site of PD. Gastrointestinal symptoms may be correlated to the occurrence and deterioration of PD[3,4]. The factors causing constipation are complex. It is not only physical weakness but also lifestyle risks such as less fluid intake[5]. Additionally, side effects of medications are responsible for many patients[3,6]. More and more evidence showed that delayed colonic transit and

peripheral parasympathetic system dysregulation are very important mechanisms[7]. The lifestyles and eating habits are also important factors. Different races and regions have different lifestyles and eating habits. In addition, studying on the gastrointestinal symptoms in PD can be conducive to understanding the pathogenesis and heterogeneity of clinical manifestations of PD. In the present study, we comprehensively screened NMS, especially constipation, in patients with PD in northwestern China and analyzed the clinical characteristics and relative factors of constipation.

MATERIALS AND METHODS

Patients

Based on a cross-sectional survey, consecutive patients who met the movement disorders society criteria for PD[8] were recruited at the First Affiliated Hospital of Xi'an Jiaotong University (Shaanxi Province, China) from March to November 2018. The secondary Parkinson's syndrome such as post-traumatic, drug-induced, and vascular parkinsonism were excluded. Patients who could not complete rating scales due to severe cognitive dysfunction and those with acute and chronic gastrointestinal diseases in the past 6 mo were excluded. The research was approved by the local ethics committee. All patients gave their consent to participate and were assessed by experienced neurologists by face-to-face interviews.

Clinical assessments

Demographic variables, such as gender, age, side of onset, education level, disease duration, medical history, motor complications, and equivalent daily dose of levodopa were recorded for all patients using a self-designed questionnaire.

Constipation was assessed based on Roman III criteria for functional constipation. The constipation severity was evaluated by Wexner score (The lowest score is 0, and the highest score is 30. The higher the score, the more severity of constipation).

The modified Hoehn-Yahr stage was used to assess severity and Unified Parkinson's disease Rating Scale (UPDRS) III was used to assess motor symptoms.

NMS were evaluated with the non-motor symptoms assessment scales (NMSS), a self-administered 30-item instrument for screening the presence NMS and incidence of each non-motor symptom. The higher the scores, the more severe the NMS.

Depression was assessed using the Hamilton depression scale (HAMD)-24 items. A score of HAMD scale-24 items ≥ 8 points suggested depression.

Anxiety was assessed using the Hamilton anxiety scale (HAMA)-14 items. A score of HAMD scale-14 items ≥ 7 points indicated anxiety.

Quality of life was assessed using the Parkinson's disease Questionnaire-39 (PDQ-39). The higher the score, the worse the quality of life.

Cognitive impairment was evaluated using the Montreal cognitive assessment (MoCA) (if educational years < 12 years, 1 point was added to the test results to correct the test bias, and < 26 points suggested cognitive dysfunction).

The tremor score was composed of item 16 in UPDRS II and items 20 and 21 in UPDRS III, and non-tremor scores included items 5, 7, and 12 to 15 in UPDRS II and items 18 to 19 and 22 to 31 in UPDRS III. The motor symptoms have two clinical subtypes: Tremor type (tremor score/non-tremor score > 1) and non-tremor type (straight-type, tremor score/non-tremor score ≤ 1).

Data analysis

Data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, United States). The Normally distributed continuous data are represented by the mean ± standard deviation (SD), and non-normally distributed data are presented by medians (quartile) and were analyzed by the Kruskal-Wallis test. Discrete variables were compared by the Chi square test. The *t*-test was used to compare the age, age of onset, UPDRS III, levodopa equivalent dose, NMSS, HAMA, HAMD, MoCA, PDQ-39, and Wexner scores between the constipation and non-constipation groups. The Kruskal-Wallis test was used to compare the incidence of constipation and one-way ANOVA was used to compare Wexner scores among different Hoehn-Yahr stages.

Pearson correlation analysis was performed to examine the correlation of constipation with sex, age, age of onset, scores of NMS, UPDRS total, UPDRS, PDQ-39, MoCA, HAMD, and HAMA, and Hoehn-Yahr stage. The unconditional logistic regression model was conducted to identify the risk factors for constipation in PD patients. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 166 subjects with PD were enrolled, including 76 women and 90 men, with a mean age of 65.92 ± 9.02 years, mean disease duration of 4.89 ± 3.93 years, and mean age at onset of 61.01 ± 9.97 years. Table 1 shows their characteristics and scores of rating scales. According to modified Hoehn-Yahr stage, 21 (12.65%) patients were in stage 1, 31 (18.67%) in stage 1.5, 56 (33.73%) in stage 2, 20 (12.05%) in stage 2.5, 28 (16.87%) in stage 3, and 10 (6.02%) in stage 4. Among them, 134 (80.72%) patients were treated with levodopa, 92 (55.42%) with dopamine agonists, 44 (26.51%) with monoamine oxidase B inhibitor, 9 (5.42%) with catechol-oxyl-methyltransferase inhibitor, 26 (15.66%) with anticholinergic drug, and 15 (9.04%) with amantadine.

Comparison of general characteristics between patients with constipation and non-constipation

Of all patients with PD enrolled, 87 (52.41%) were accompanied with constipation. Among constipation patients, 30 (34.48%) had constipation occurring before 6.30 ± 5.06 years at onset of motor symptoms. The age of patients, disease duration, Hoehn-Yahr grade, duration of levodopa treatment, incidence of motor complications, scores of UPDRS total and UPDRS III, NMSS, HAMD, HAMA, and PDQ-39 in the constipation group were significantly higher than those in the non-constipation group ($P < 0.05$), but there was no statistical difference in the scores of MoCA, clinical types, or medications between the two groups ($P > 0.05$). Details are given in Table 2.

Incidence of depression, anxiety, and cognitive impairment between patients with and without constipation

Compared to the non-constipation group, there was a higher incidence of depression in patients with constipation (46.84% *vs* 64.37%, $P < 0.05$). But there was no statistical difference in the incidence of anxiety and cognitive impairment between the two groups ($P > 0.05$). Detailed data are shown in Table 3.

Incidence and severity of constipation in patients of different Hoehn-Yahr stages

According to the modified Hoehn-Yahr stage, there were 52 patients in stage 1-1.5, 76 in stage 2-2.5, 28 in stage 3, and 10 in stage 4. Although the incidence of constipation did not increase while Hoehn-Yahr stage increased ($P > 0.05$), the severity of constipation increased while Hoehn-Yahr stage increased ($P < 0.05$). Detailed results are shown in Table 4.

Risk factors for constipation

Pearson correlation analysis showed that constipation was moderately positively correlated with age, Hoehn-Yahr stage, NMSS scores, UPDRS III and total scores, PDQ-39 scores, MoCA scores, HAMD scores, and HAMA scores (r = 0.255, 0.172, 0.361, 0.194, 0.221, 0.237, 0.238, and 0.207, respectively, $P < 0.05$). Results are shown in Table 5. Other variables such as sex, age at onset, MoCA scores, and medication did not have a correlation with constipation ($P > 0.05$).

Using constipation as the dependent variable, and factors such as age, disease duration, Hohen-Yahr stages, UPDRS III scores, duration of medication, depression and anxiety, and NMSS score as independent variables, the logistic regression analysis demonstrated that only NMSS score was an independent risk factor for constipation ($P < 0.001$).

DISCUSSION

Traditionally, cytotoxicity and Lewy body (LB) formation mediated by α-synuclein (α-SYN) was preferential in the pathogenesis of PD. In fact, the pathological changes of PD are extensive. Besides the brainstem, abnormal α-SYN also deposits in many other parts of the body including the intestine, pancreas, heart, salivary glands, and skin. PD is a syndrome of multiple organ dysfunction involving dopaminergic, adrenergic, serotoninergic, and cholinergic pathways[4]. Therefore, the clinical manifestations of PD include varieties of NMS such as olfactory hypothyroidism, cognitive disorders, sleep disorders, depression, constipation, and other motor symptoms[1]. We have realized the negative impact of NMS on quality of life. For some PD patients, disability may be more severe in NMS than dyskinesia[9]. Although PD has been recognized for 200

Table 1 Clinical characteristics of the subjects

Characteristic	Value	Characteristic	Value
Patients *n*	166	Hoehn-Yahr stage *n* (%)	
Male *n* (%)	90 (54.22)	Stage 1	21 (12.7)
Mean age ± SD (yr)	65.92 ± 9.02	Stage 1.5	31 (18.7)
Hypertension *n* (%)	60 (36.14)	Stage 2	56 (33.7)
Diabetes *n* (%)	14 (8.43)	Stage 2.5	20 (12.0)
Coronary heart disease *n* (%)	16 (9.64)	Stage 3	28 (16.9)
Family history of PD *n* (%)	8 (4.82)	Stage 4	10 (6.0)
Mean age at onset ± SD (yr)	61.01 ± 9.97	Mean scores of scale ± SD	
Disease duration (yr)	4.89 ± 3.93	UPDRS total	39.16 ± 18.39
Clinical type *n* (%)		UPDRS III	21.79 ± 11.72
Tremor	91 (54.82)	Wexner	4.29 ± 5.30
Non-tremor	75 (45.18)	HAMD	10.00 ± 8.61
Motor complications *n* (%)		HAMA	11.18 ± 10.27
Symptom fluctuation	51 (30.72)	MoCA	19.56 ± 5.75
Dyskinesia	25 (15.06)	PDQ-39	35.66 ± 24.06
Medication *n* (%)		NMSS	49.89 ± 32.55
Levodopa	134 (80.72)		
Dopamine agonist	92 (55.42)		
MAO-B inhibitor	44 (26.51)		
COMT inhibitor	9 (5.42)		
Anticholinergic	26 (15.66)		
Amantadine	15 (9.04)		

PD: Parkinson's disease; UPDRS: Unified Parkinson's disease Rating Scale; HAMD: Hamilton depression scale; HAMA: Hamilton anxiety scale; MAO: Monoamine oxidase; COMT: Catechol-o-methyltransferase; NMSS: Non-motor symptoms assessment scales; PDQ-39: Parkinson's disease questionnaire-39; MoCA: Montreal cognitive assessment.

years, the mechanisms of its pathogenesis and treatments still need to be explored, especially outside the central nervous system[10]. The present research showed that NMS are common during the whole course of PD. Almost all PD patients complained of at least one NMS, with an average of eight NMS[11]. NMS may involve multiple regions and neurotransmitter disorder in the pathogenesis of PD[1]. A Korean population study showed that gastrointestinal symptoms were widespread even in patients with early PD without treatment, with the incidence of constipation being 46.3%[12]. Some studies have shown that before the midbrain dopaminergic neurons were affected, a variety of NMS could occur, which was associated with a higher risk of developing PD. It was suggested that NMS may be considered an early clinic manifestation in PD patients[13]. Therefore, constipation, one of NMS, in PD patients may be an intrinsic symptom.

Our findings confirm that constipation (52.41%) is a common NMS in PD with a relatively high frequency. Constipation had occurred in about 34.48% of patients for a mean of 6.3 years before the onset of motor symptoms. The incidence of constipation in patients with PD has been reported to be 4%-71%, mostly at 24%-63%, some even up to 80%[2,14]. The reason for the inconsistencies in epidemiological surveys may be related to differences in study population and inclusion criteria. A prospective clinical study found that people who had defecated more than once a day had a 2.7 times risk of developing PD after 10 years of follow-up than those who defecated less than once a day[15]. Pathological studies also demonstrated that patients defecated more than once a day had a four-fold increase in the probability of subsequent Lewy body deposition compared with those who defecated less than once a day[16]. These findings suggested

Table 2 Comparison of general characteristics between the constipation and non-constipation groups

	Constipation	Non-constipation	*t*/χ2 value	*P* value
Male, *n* (%)	52 (59.77)	38 (48.10)	2.271	0.132
Mean age ± SD (yr)	68.10 ± 8.16	63.51 ± 9.42	3.355	0.001
Mean age at onset ± SD (yr)	62.34 ± 9.38	59.56 ± 10.52	1.796	0.074
Mean disease duration ± SD (yr)	5.66 ± 4.41	4.00 ± 3.12	2.732	0.007
Clinical types, *n* (%)				
Tremor	46 (52.87)	45 (56.96)		
Non-tremor	41 (47.13)	34 (43.04)	0.279	0.597
Hoehn-Yahr stage (median, quartile)	2.0 (1.5, 3.0)	2.0 (1.5, 2.5)	-2.451	0.014
Mean UPDRS total scores ± SD	43.02 ± 19.57	34.90 ± 16.05	2.889	0.004
Mean UPDRS III scores ± SD	23.94 ± 12.03	19.41 ± 10.97	2.512	0.013
Mean levodopa equivalent dose ± SD (mg/d)	468.17 ± 357.98	441.92 ± 428.78	0.416	0.678
Mean daily dose of levodopa ± SD (mg/d)	500.41 ± 326.55	430.91 ± 163.93	1.491	0.138
Mean levodopa medication times ± SD (mo)	53.43 ± 49.56	29.25 ± 35.77	3.265	0.001
Medication, *n* (%)				
Levodopa	73 (83.91)	61 (77.22)	1.192	0.275
Dopamine agonist	53 (60.92)	39 (49.37)	2.273	0.135
MAO-B inhibitor	23 (26.44)	21 (26.58)	< 0.001	0.983
COMT inhibitor	7 (8.05)	2 (2.53)	2.455	0.117
Anticholinergic	14 (16.09)	12 (15.19)	0.026	0.873
Amantadine	7 (8.05)	8 (10.13)	0.218	0.641
Motor complications, *n* (%)				
Symptom fluctuation	33 (37.93)	18 (22.78)	4.463	0.035
Dyskinesia	18 (20.69)	7 (8.86)	4.529	0.033
NMSS scores	61.05 ± 32.95	37.59 ± 27.42	4.928	0.000
HAMD scores	11.94 ± 8.59	7.86 ± 8.16	3.113	0.002
HAMA scores	13.20 ± 10.37	8.96 ± 9.75	2.688	0.008
MoCA scores	19.71 ± 5.48	19.36 ± 6.11	0.374	0.709
PDQ-39 scores	41.07 ± 25.58	29.69 ± 20.84	3.104	0.002

UPDRS: Unified Parkinson's disease Rating Scale; MAO: Monoamine oxidase; COMT: Catechol-o-methyltransferase; NMSS: Non-motor symptoms assessment Scales; HAMD: Hamilton depression scale; HAMA: Hamilton anxiety scale; MoCA: Montreal cognitive assessment; PDQ-39: Parkinson's disease questionnaire-39.

that constipation may promote the risk of PD. Although constipation is universal in patients with PD, the clinical manifestations are diverse.

Lifestyles especially food habits are responsible for constipation in PD patients, but not a critical factor. Constipation patients with PD consumed less water fluid and fewer fresh fruits, raw vegetables, fish, meats, *etc*.[17]. The incidence of constipation in PD patients is higher in Asian populations than in Western populations. According to surveys in Asian countries (such as in China, South Korea, and India), the difference may be related to diet habit, exercise, nutritional status, gut flora, education, and drug treatment[18].

Constipation in PD patients is directly related to its pathogenesis. According to the Braak staging scheme, the PD lesions do not start from the dopaminergic neurons in the midbrain. The olfactory bulb, the glossopharyngeal nerve, the vagus nerve dorsal

Table 3 Incidence of depression, anxiety, and cognitive impairment between the constipation and non-constipation groups

	n	Anxiety (%)	Depression (%)	Cognitive impairment (%)
Constipation	87	55 (63.22)	56 (64.37)	71 (81.61)
Non-constipation	79	40 (50.63)	37 (46.84)	63 (79.75)
χ^2		2.695	5.187	0.092
P		0.115	0.029	0.845

Table 4 Comparison of incidence and severity of constipation in different modified Hoehn-Yahr grades (%, ± s)

Grade	1-1.5	2-2.5	3	4	χ^2/F	*P* value
n	52	76	28	10		
Constipation	22 (42.31)	41 (53.95)	16 (57.14)	8 (80.00)	5.470	0.140
Wexner score	6.73 ± 4.14	6.76 ± 3.58	11.19 ± 5.38	13.50 ± 2.98	10.138	< 0.001

Table 5 Correlations of constipation and different related scale scores

	r	*P* value
Age	0.255	0.001
Modified Hoehn-Yahr stage	0.172	0.027
NMMS scores	0.361	< 0.001
UPDRS III scores	0.194	0.013
UPDRS total scores	0.221	0.004
PDQ-39 scores	0.237	0.002
HAMD scores	0.238	0.002
HAMA scores	0.207	0.008

NMSS: Non-motor symptoms assessment scales; UPDRS: Unified Parkinson's disease Rating Scale; PDQ-39: Parkinson's disease questionnaire-39; HAMD: Hamilton depression scale; HAMA: Hamilton anxiety scale.

nucleus, and the intestinal intermuscular nerve plexus may be involved at the early stage of the disease[19]. Recent studies have shown that the pathological changes of PD may be changed through the intestinal microbial flora to the intestinal nervous system. Intestinal microbial flora changes can result in misfolding of α-SYN. The pathological α-SYN could be absorbed into the intestinal plexus by the intestinal mucosa from the myenteric plexus, and then retrogradely transmitted to the brain stem and brain along the vagus nerve, which may result in dopaminergic property alteration in the substantial nigra. In addition, the intestinal microbial flora may have a direct effect on host neural activity through the production of hormones and neurotransmitters, such as monoamines, GABA, and short-chain fatty acids. These products could lead to central nervous system glial activation and promote changes in inflammatory signaling molecules and oxidative stress, which may be the basic mechanisms of neurodegeneration in PD[3,20]. In the early stage of PD, the Lewy body has been found to be deposited in the submucosal plexus of the intestine[21]. It has been also reported that the incidence of PD in constipation patients was 3.3-4.2 times higher than those without constipation, and the severity of constipation was closely associated with the occurrence of PD[22]. We therefore postulated that constipation may be a precursor sign in the early stage of PD.

It has been found that there is a higher incidence of anxiety and depression in PD patients. The prevalence of depression varies from 2.7% to 90%[23,24], which may be attributed to differences of methodology or diagnostic criteria. A report indicated that the prevalence of depression was 11.17% and anxiety was 25.81% in Chinese PD patients[25]. Our findings show that the prevalence of depression and anxiety in PD patients was higher, and patients with constipation were more prone to depression but

without anxiety and cognitive impairment. Hawkes *et al*[20] have proved that the pathogenesis of PD is not only associated with the substantia nigra, but also related to the raphe nucleus and locus coeruleus before the presence of motor symptoms in PD[20]. It was suggested that serotonin and noradrenaline were involved in the occurrence of depression in PD[9].

Univariate analysis showed that the PD patients with constipation had older age, longer disease duration, more severe motor symptoms, and higher Hoehn-Yahr stages. The causes and mechanisms of constipation with PD are still unclear. The decline of sphincter function and anti-PD drugs such as levodopa and benzhexol are important factors. Other factors such as abdominal muscle weakness, decreased water intake, decreased activity, and bed rest also can increase the risk of constipation occurrence. In recent years, gut-first theory of PD exactly explained the causes of gastrointestinal symptoms. In addition to central nervous system degeneration, PD also undergoes degeneration of the enteric nerves, which is even earlier than that of the central nervous system. During the progression of PD, the changes of intestinal microbial flora could cause changes in the permeability of the intestinal mucosa and intestinal inflammation, which may result in the misfolding of α-SYN, and the misfolded α-SYN is deposited in neurons of intestinal mucosal and parasympathetic neurons of the spinal cord. Subsequently, dysfunction of intestinal neurons could cause delayed colonic transit and outlet obstruction, and finally resulted in constipation[26]. In addition, the degeneration of the dorsal vagus nucleus in PD patients may lead to autonomic nervous dysfunction, exacerbation of gastrointestinal dysfunction, and failure of defecation-related muscle contraction and relaxation. Dysfunction of the pelvic floor and anorectal sphincter is another cause[2]. The incidence of depression in patients with constipation is also increased. Depression may result in decreased ability of physical activity, daily activities, appetite, or gastrointestinal function, and cause constipation to develop and worsen as the disease progresses[27]. Besides, constipation in patients having taken levodopa and dopamine agonists may be related to the stimulation of peripheral dopamine receptors by the drug[28]. The occurrence of motor complications is closely related to the duration of the disease and the treatment effect of levodopa. With the prolongation of the course of disease, the progression of the disease, and the dosage of the drug treatment, the adverse drug reactions may increase further. Constipation is a common adverse reaction of many PD drugs, especially anticholinergics and dopamine agonists[29]. Our study showed that only NMS score is an independent risk factor for constipation by multivariate regression analysis, while medications are not an independent factor. Therefore, constipation is assumed to be an inherent symptom of PD rather than other risk factors.

Constipation in PD patients is widespread throughout the whole course of disease, even before motor symptoms. Thus, it is important to explore the possibility of constipation as a clinical prodromal biomarker for PD. It still needs further investigation on the mechanisms of clinical features and the treatments[30]. The study of gastrointestinal function can deepen the understanding of gut-origin theory of PD.

The current study has some limitations that should be pointed out. First, this is an observational, descriptive, survey study and our sample size is relatively modest. Moreover, the research subjects mainly from outpatients may lead to selective bias of the global PD population. Second, depression, anxiety, and cognition are only suggestibility of state due to the rating scale but not a formal clinical diagnosis. Finally, some variables such as adverse lifestyle and food habits of participants are not taken into account. Follow-up study about constipation in larger PD cohorts would provide accurate specific scales for different variables and a more comprehensive overview.

CONCLUSION

Our findings confirm that constipation has a relatively high frequency in patients with PD. PD patients with constipation have a higher incidence of depression, which leads to worse quality of life.

ARTICLE HIGHLIGHTS

Research background

Parkinson's disease (PD) is a neurodegenerative disorder and causes motor symptoms including resting tremor, akinesia, and rigidity. Recently, the focus of clinical research

on PD is shifting to non-motor symptoms (NMS). Among all NMS, constipation is particularly common, but the reason why PD patients are prone to constipation is still unclear. In addition to physical weakness and other factors, lifestyles and eating habits are important factors as well. The prevalence and influencing factors of constipation may vary among different populations.

Research motivation

At present, the mechanisms and risk factors underlying constipation in patients with PD are still uncertain. Although the prevalence of constipation in Chinese patients with PD has been reported before, it may vary among different populations due to the different lifestyles and eating habits. Therefore, we need to understand the prevalence and influencing factors of constipation in the PD population in northwest China.

Research objectives

To investigate the prevalence and risk factors of constipation in a cohort study of Chinese patients with PD.

Research methods

Based on accepted diagnostic criteria and a series of clinic rating scales, which contained modified Hoehn-Yahr stage, Unified PD Rating Scale (UPDRS) III, non-motor symptoms assessment scale (NMSS), Hamilton depression scale (HAMD), Hamilton anxiety scale (HAMA), Parkinson's disease Questionnaire-39 (PDQ-39), Montreal cognitive assessment, etc. The incidence and related factors of constipation was identified based on a retrospective survey. All subjects were recruited from March to November 2018 at the Department of Neurology of the First Affiliated Hospital of Xi'an Jiaotong University. In the following statistical analyses, *t*-test, spearman correlation, nonparametric test, one-way ANOVA, and unconditional logistic regression analysis were used.

Research results

In this study, 52.41% of patients were accompanied with constipation, and 34.48% had constipation occurring 6.30 ± 5.06 years before the onset of motor symptoms. The age of patients, disease duration, Hoehn-Yahr stage, duration of levodopa treatment, incidence of motor complications, scores of UPDRS total and UPDRS III, NMSS, HAMD, HAMA, and PDQ-39 in the constipation group were significantly higher than those in the non-constipation group ($P < 0.05$). Compared to the non-constipation group, there was a higher incidence of depression in patients with constipation (46.84% *vs* 64.37%, $P < 0.05$). The logistic regression analysis demonstrated that only NMSS score was an independent risk factor for constipation ($P < 0.001$).

Research conclusions

Our findings confirm that constipation has a relatively high frequency in patients with PD. PD patients with constipation have a higher incidence of depression, which leads to worse quality of life.

Research perspectives

Constipation is a common symptom in PD patients and reduces their quality of life. It should attract more attention in the future studies.

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