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The non-motor symptoms of Parkinson's disease of different motor types in early stage

L.-L. ZHONG[1,3], Y.-Q. SONG[2], H. CAO[1], K.-J. JU[1], L. YU[3]

[1]Department of Neurology, Huai'an First People's Hospital, Nanjing Medical University, Huai'an, Jiangsu, P.R. China
[2]Department of Radiation Oncology, Huai'an First People's Hospital, Nanjing Medical University, Huai'an, Jiangsu, P.R. China
[3]Department of Hematology, Huai'an First People's Hospital, Nanjing Medical University, Huai'an, Jiangsu, P.R. China

Abstract. – OBJECTIVE: We aimed to compare the different non-motor symptoms of different motor phenotype Parkinson's disease (PD) at an early stage.

PATIENTS AND METHODS: From January 2013 to November 2016, 120 cases of PD patients who were hospitalized in Neurology Department of the First Hospital of Huai'an in Jiangsu Province and 120 cases of healthy controls with matched age and gender, were included into the research. PD patients were administered with Non-Motor symptom questionnaire (NMSQuest), the Unified Parkinson's Disease Rating Scale III (UPDRS-III), the Mini-Mental State Examination score (MMSE), the Hoehn-Yahr classification, the MoCA, and GDS-15. The relationship between NMS burden and PD subtypes, age, gender and disease severity were examined using linear regression models. The prevalence of each NMS among different PD motor subtypes was analyzed using x^2 test.

RESULTS: Compared with the healthy controls, PD patients had a higher number of NMS. The prevalence of NMS in postural instability gait difficulty (PIGD) group is higher than that in tremor dominant (TD) group. There is no significant correlation between age, gender, MMSE scores, MoCA scores and the number of NMS. PD patients with higher UPDRS-III scores and a longer course of disease had a higher prevalence of NMS.

CONCLUSIONS: NMS is also common in PD patients at an early stage. The PIGD group who have more axial injuries and more severe motor symptoms, have a higher risk of NMS burden than PD patients in TD group.

Key Words:
Parkinson's disease, Non-motor symptom, Different motor types, Postural instability gait difficulty, Tremor dominant.

Introduction

As a common neurodegeneration, the motor symptoms of Parkinson's disease (PD) can be detected and controlled during the early stage. According to Barone et al[1] 98.6% of PD patients have non-motor symptoms (NMS) including cognitive impairment, depression, anxiety, sleep disorders, bowel and/or bladder problems, pain and other autonomic disturbances, which have been gradually noticed in recent years and are regarded as the important constituent parts of PD[2,3]. With the progression of disease, NMS have serious influence on the prognosis and the quality-of-life (QOL) of PD patients[4,5]. Existing researches mainly focused on cognitive impairment, anxiety and sleep disorders in PD patients[6-9]. However, few researches have explored the correlation between NMS and different motor phenotypes during early stage of PD.

Motor phenotypes in PD can be divided into postural instability gait difficulty (PIGD) and tremor dominant (TD) types[10]. Patients in PIGD group is characterized by more axial symptoms, loss of postural reflexes and freezing of gait, which made PIGD patients more disabled in comparison to TD patients[10,11]. Beside, bulbar dysfunctions is also more common in the PIGD group[11]. These raise the concern that NMS might be prominent in the PIGD subtype. In recent years, scholars have found that the patients in PIGD subtype without cognitive impairment have more NMS and poorer QOL when compared with the patients in TD subtype[12]. Recently, NMSQuest has been effectively applied to the screening and evaluation of NMS in PD patients. The NMS Quest is a 30-item screening questionnaire to be used by the patient or caregiver as a screening tool. It contains ten domains to cover gastrointestinal symptoms, urinary tract symptoms, sexual functions, cardiovascular issues, apathy/attention/memory concerns, hallucinations/delusions, depression/anxiety, sleep problems/fatigue, pain, and miscellaneous complaints such as diplopia and weight changes[13].

Corresponding Author: Liang Yu, MD; e-mail: liangyu163mail@163.com

Therefore, in this study, we aimed to explore the relationship between NMS and motor subtypes of PD during early stage. In addition, the correlation between NMS and age, gender, MMSE scores, MoCA scores, UPDRS-III scores as well as course of disease, were explored.

Patients and Methods

Patients

From January 2013 to November 2016, 120 cases of PD patients who were hospitalized in Neurology Department of the First Hospital of Huai'an in Jiangsu Province and 120 cases of healthy controls with matched age and gender, were collected. The inclusion criteria: (1) patients should be diagnosed as PD in accordance with the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria; (2) patients should sign the informed consent form, and have no significant cognitive impairments and can finish the questionnaires independently; (3) patients should be evaluated as grade 1-2 by Hoehn-Yahr scoring. The exclusion criteria: (1) dementia or significant memory disorder, which is defined as mini-mental state examination (MMSE) score <24; (2) Parkinsonism and Parkinson-plus syndromes induced by cerebrovascular disease, intoxication and drugs. This study was approved by the Ethical Committee of our hospital.

Questionnaires

General information of patients including name, gender, age, course of disease, starting time for medication and medication condition via history collection and questionnaires were collected. The Non-Motor symptom questionnaire (NMSQuest) was used to assess the NMS. NMSQuest includes 30 items on 10 aspects, with two answers of "Yes" or "No". Any "Yes" is calculated as 1 score; the total score is 30. Higher scores illustrate more NMS symptoms. The Unified Parkinson's Disease Rating Scale III (UPDRS-III) was used to assess the motor symptoms. The Mini-Mental State Examination score (MMSE), the Montreal Cognitive Assessment Scale (MoCA) and Geriatric Depression Scale (GDS-15) were used to assess the cognitive function of patients. Disease severity grading was assessed by the Hoehn-Yahr classification grating (H-Y), in which H-Y grade 1-2 is defined as the early stage disease.

Statistical Analysis

The SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) is adopted for analysis. The measurement data is expressed as mean ± standard deviation. Comparison for measurement data between groups is performed by *t*-test, while comparison for enumeration data between groups is performed by x^2 test. The prevalence of each NMS among different PD motor subtypes was analyzed using x^2-test. The correlation between factors and NMS is analyzed by regression models. Statistical significance was considered when $p<0.05$.

Results

General Conditions of Research Population

Comparison of baseline characteristics between early PD patients and healthy controls (HC) were shown in Table I. In this study, 120 cases of PD patients in early stage were collected, including 67 males (55.8%) aging 60-80 years old (70.06 ± 1.06 years), and 53 females (44.2%) aging 53-80 years old (67.89 ± 1.12 years). The course of disease was between 1 month to 2 years. Meanwhile, 120 healthy controls seeking for medical advice during the same period were collected, including 65 males (54.2%) aging 60-82 years (69.43 ± 0.84 years), and 55 females (45.8%) aging 50-80 years old (66.45 ± 0.95 years). There was no significant difference between the two groups about gender, age and educational background (Table I, $p>0.05$). Meanwhile, PD patients and healthy controls were surveyed by MMSE, MoCA and GDS-15 scoring.

PD Patients Developed more NMS than Healthy Controls

The comparison of NMS occurrence between PD group and HC group is shown in Table II. The total number of NMS of the PD group is higher than that of the HC group ($p<0.0001$). Specifically, the prevalence of drooling, dysphagia, constipation, urgent urination, sexual dysfunction, OH, memory decline, depression, anxiety, insomnia, vivid dreams, REMBD, RCS and pain in PD group are significantly higher than that of the HC group ($p<0.0001$ for all). For nausea, fecal incontinence, weight changes, nocturia and leg swelling, the prevalence in PD group is lower than that of the HC group without a significant difference.

Table I. Comparison of baseline characteristics between early PD patients and healthy controls.

Projects	PD (n=120)	HC (n=120)	Test value	*p*
Male (N, %)	67 (55.8)	65 (54.2)	X^2=0.07	0.79
Age (years)	69.10 ± 0.78	68.07 ± 0.78	t = 1.03	0.31
Education (years)	10.87 ± 0.40	11.13 ± 0.77		0.76
Disease course (years)		3.90 ± 0.35	no	
UPDRS-III score		8.28 ± 0.49	no	
H-Y grade 1 (N, %)		49 (40.8)	no	
H-Y grade 2 (N, %)		71 (59.2)	no	
Levodopa effective dose (mg)	180.5 ± 102.3	no		
MMSE score	26.21 ± 0.13	26.74 ± 0.13		0.0041
MoCA score	25.93 ± 0.12	26.32 ± 0.087		0.0103
GDS-15 score	3.80 ± 0.25	1.67 ± 0.29		< 0.0001

Table II. Comparison of NMS between early PD patients and healthy control.

Projects	PD (n=120)	HC (n=120)	Test value	*p*
Median of NMS total Numbers (Interquartile)	5.5 (4.5)	2.0 (1.67)	Z=-8.87	< 0.0001
Drooling	25 (20.8)	5 (4.17)	X2=17.30	< 0.0001
Dysphagia	25 (20.8)	2 (1.67)	X2=22.08	< 0.0001
Nausea	11 (9.17)	9 (7.5)	X2=0.24	0.6267
Constipation	35 (29.2)	5 (4.17)	X2=27.00	< 0.0001
Fecal incontinence	5 (4.17)	4 (3.33)	X2=0.12	0.734
Poor bowel empty	20 (16.7)	6 (5.0)	X2=8.45	0.0036
Anosmia	14 (11.67)	3 (2.5)	X2=7.66	0.0056
Weight changes	11 (9.17)	6 (5.0)	X2=1.58	0.2084
Urinary urgency	54 (45.0)	15 (12.5)	X2=30.94	< 0.0001
Nocturia	68 (56.7)	55 (45.8)	X2=2.82	0.0932
Hyposexuality	28 (23.3)	8 (6.67)	X2=13.07	0.0003
Sexual dysfunction	41 (34.2)	10 (8.33)	X2=23.93	< 0.0001
Orthostatic hypotension (OH)	38 (31.7)	7 (5.8)	X2=26.28	< 0.0001
Fall because of OH	15 (12.5)	2 (1.7)	X2=9.60	0.002
Leg swelling	16 (13.3)	12 (10.0)	X2=0.65	0.4212
Memory decline	44 (36.7)	16 (13.3)	X2=17.42	< 0.0001
Poor concentration	31 (25.8)	4 (3.3)	X2=13.49	0.0002
Depression	38 (31.7)	9 (7.5)	X2=22.25	< 0.0001
Apathy	20 (16.7)	6 (5.0)	X2=8.45	0.0036
Delusion	5 (4.17)	0 (0)	X2=5.11	0.0238
Hallucination	11 (8.33)	0 (0)	X2=11.53	0.0007
Anxiety	33 (27.5)	6 (5.0)	X2=22.32	< 0.0001
Diplopia	14 (11.67)	4 (3.33)	X2=6.01	0.0143
Sweating	27 (22.5)	7 (5.83)	X2=13.71	0.0002
Hypersomnolence	16 (13.3)	1 (0.833)	X2=14.24	0.0002
Insomnia	53 (44.2)	10 (8.33)	X2=39.80	< 0.0001
Vivid dreams	28 (23.3)	2 (1.67)	X2=25.75	< 0.0001
REM behavior disorders (REMBD)	32 (26.7)	8 (6.67)	X2=17.28	< 0.0001
Restless legs syndrome (RLS)	37 (30.8)	9 (7.5)	X2=21.08	< 0.0001
Pain	39 (32.5)	4 (3.33)	X2=34.71	< 0.0001

PD Patients in PIGD Group Developed more NMS than TD Group

The UPDRS-III score of the PIGD group is significantly higher than that of the TD group (t=4.454, df=93 p<0.0001), while the MMSE and the MoCA scores of the TD group are significantly higher than that of the PIGD group (t=11.52, df=93, p<0.0001, t=8.794 df=93, p<0.0001). After the adjustment to course of disease and UPDRS-III scores, the total prevalence of NMS in the PIGD group is higher than that of the TD group (t=2.998 df=93, p=0.0035), and the comparison on NMS between the two groups is shown in Table III. Among those, the prevalence of fecal incontinence, leg swelling and delusion between the PIGD group and TD group is no significantly different.

Table III. Comparison of NMS of early PD patients between different subtypes.

Projects	PD (n=120)	TD (n=37)	PIGD (n=83)	Test value	p
Drooling (%)	25 (20.8)	2 (5.41)	23 (27.7)	X^2=7.720	0.0055
Dysphagia (%)	25 (20.8)	1 (2.70)	24 (28.9)	X^2=10.66	0.0011
Nausea (%)	11 (9.17)	0 (0)	11 (12.3)	X^2=5.398	0.0202
Constipation(%)	35 (29.2)	4 (10.8)	31 (37.3)	X^2=8.724	0.0031
Fecal incontinence(%)	5 (4.17)	0 (0)	5 (6.02)	X^2=2.388	0.1223
Poor bowel empty (%)	20 (16.7)	2 (5.40)	18 (21.7)	X^2=4.884	0.0271
Anosmia (%)	14 (11.67)	1 (2.70)	13 (15.67)	X^2=4.171	0.0411
Weight loss (%)	11 (9.17)	0 (0)	10 (12.0)	X^2=4.863	0.0274
Urinary urgency (%)	54 (45.0)	6 (16.2)	49 (59.0)	X^2=14.431	0.0001
Nocturia (%)	68 (56.7)	8 (21.6)	60 (72.3)	X^2=26.76	< 0.0001
Hyposexuality (%)	28 (23.3)	2 (5.41)	26 (31.3)	X^2=9.611	0.0019
Sexual dysfunction (%)	41 (34.2)	5 (13.5)	36 (43.4)	X^2=10.14	0.0014
OH (%)	38 (31.7)	5 (13.5)	33 (39.8)	X^2=8.147	0.0043
Fall because of OH (%)	15 (12.5)	1 (2.70)	14 (16.9)	X^2=4.695	0.0303
Leg swelling (%)	16 (13.3)	2 (5.4)	14 (16.9)	X^2=2.910	0.0881
Memory decline (%)	44 (36.7)	5 (13.5%)	39 (32.5)	X^2=12.89	0.0003
Poor concentration (%)	31 (25.8)	3 (8.1%)	28 (33.7%)	X^2=9.133	0.0025
Depression (%)	38 (31.7)				
Apathy (%)	20 (16.7)	2 (5.4%)	18 (21.7%)	X^2=5.096	0.024
Delusion (%)	5 (4.17)	0 (0%)	5 (6.02%)	X^2=2.388	0.1223
Hallucination (%)	11 (8.33)	0 (0%)	11 (12.3%)	X^2=5.540	0.0186
Anxiety (%)	33 (27.5)	3 (8.1%)	30 (36.1%)	X^2=10.49	0.0012
Diplopia (%)	14 (11.67)	1 (2.70%)	13 (15.7%)	X^2=4.171	0.0411
Sweating (%)	27 (22.5)	2 (5.4%)	25 (30.1%)	X^2=8.965	0.0028
Hypersomnolence (%)	16 (13.3)	1 (2.70%)	15 (18.1%)	X^2=5.232	0.0222
Insomnia (%)	53 (44.2)	5 (13.5%)	48 (57.8%)	X^2=20.38	< 0.0001
Vivid dreams (%)	28 (23.3)	2 (5.41%)	26 (31.3%)	X^2=9.611	0.0019
REMBD (%)	32 (26.7)	2 (5.41%)	30 (36.1%)	X^2=12.37,	0.0004
RLS (%)	37 (30.8)	3 (8.1%)	34 (41.0%)	X^2=12.95	0.0003
Pain (%)	39 (32.5)	3 (8.2%)	36 (43.4%)	X^2=14.51	0.0001

Correlated Factors of NMS in PD Patients

To determine whether the NMS in PD were affected by gender, age, disease duration, severity of PD, or cognitive status, univariate linear regression analyses were performed. The univariate analyses showed that age, gender, MMSE and MoCA did not correlate with NMS. In contrast, disease duration and disease severity (UPDRS-III) were significant predictors of NMS (p<0.0001 for both). The PD patients with higher UPDRS-III scores and longer course of disease have higher prevalence of NMS (Table IV).

Discussion

NMS is frequently seen in early stage of PD, which has influence on QOL (quality of life) of patients, or even leads to disability[14]. However, these NMS are often ignored. Presently, the PD NMS have been gradually noticed. However, there are only a few literature on NMS and different PD motor subtypes. In our present study, we found that the UPDRS-III score of the PIGD group is significantly higher than that of the TD group, while the MMSE and the MoCA scores of the TD group are significantly higher than that of the PIGD group. After the adjustment to course of disease and UPDRS-III scores, the prevalence of NMS in the PIGD group is higher than that of the TD group, except for fecal incontinence, leg swelling, and delusion. These results were consistent with the previous research[15]. At the same time, we found that the PD patients with higher UPDRS-III scores longer course of disease have higher prevalence of NMS, which is also consistent to the research findings of overseas researchers[15].

Table IV. Correlated factors of NMS in PD patients.

	R2	p
Gender	0.000871	0.749
Age	0.01499	0.1828
PD duration	0.8268	< 0.0001
UPDRSIII	0.9528	< 0.0001
MMSE	0.006528	0.3928
MoCA	0.004545	0.476

The patients of the PIGD group often show more axial damages, with unfavorable therapeutic effect with dopamine[16]. According to the comparison between the two subtypes, the patients of the PIGD group have poorer prognosis and more ball functional disorder, as well as abnormal postures and treads compared with the TD group[17]. The UPDRS-III scores of the PIGD group are significantly higher than that of the TD group. Besides, the prevalence of NMS in PIGD group is higher than that of the TD group. Higher prevalence of NMS resulted in poorer QOL, which is more severe than motor symptoms. Recently, a vertical cohort research down by the Parkinson's Disease Research Center showed that the patients in PIGD group have more axial symptoms and higher NMS-induced mortality rate[18].

Although NMS is regarded as the result of non-dopamine system disorder, a lot of document researches find that the dopamine system disorder is also involved in the physio pathological mechanism of NMS[19,20]. This is supported by the efficacy of dopamine treatment for NMS, such as the treatment of depression by pramipexole and the treatment of quick eye moving sleep disorder with dopamine acceptor agonist[19,21]. In our study, we found that the MMSE and MoCaA scores of the PIGD group are significantly lower than that of the TD group, which is consistent with the previous study[15].

Conclusions

We showed that PD patients in early stage developed more NMS than healthy controls. The PIGD, but not the TD subtype, shows higher prevalence of NMS. In addition, we observed that NMS in PD patients was related to disease severity (UPDRS-III score) and course of disease, but not related to age, gender, MMSE and MoCA scores.

Conflict of Interest

The Authors declare that they have no conflict of interest.

References

1) Garcia-Ruiz PJ, Chaudhuri KR, Martinez-Martin P, Non-motor symptoms of Parkinson's disease. A review...from the past. J Neurol Sci 2014; 338: 30-33.
2) Petschow C, Scheef L, Paus S, Zimmermann N, Schild HH, Klockgether T, Boecker fMRI Study. PLoS One 2016; 11: e0164607.
3) Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, Bottacchi E, Cannas A, Ceravolo G, Ceravolo R, Cicarelli G, Gaglio RM, Giglia RM, Iemolo F, Manfredi M, Meco G, Nicoletti A, Pederzoli M, Petrone A, Pisani A, Pontieri FE, Quatrale R, Ramat S, Scala R, Volpe G, Zappulla S, Bentivoglio AR, Stocchi F, Trianni G, Dotto PD; PRIAMO study group. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord 2009; 24: 1641-1649.
4) Kasten M, Kertelge L, Tadic V, Brüggemann N, Schmidt A, van der Vegt J, Siebner H, Buhmann C, Lencer R, Kumar KR, Lohmann K, Hagenah J, Klein C. Depression and quality of life in monogenic compared to idiopathic, early-onset Parkinson's disease. Mov Disord 2012; 27: 754-759.
5) Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord 2008; 23: 837-844.
6) Burn DJ, Landau S, Hindle JV, Samuel M, Wilson KC, Hurt CS, Brown RG; PROMS-PD Study Group. Parkinson's disease motor subtypes and mood. Mov Disord 2012; 27: 379-386.
7) Aygun D, Turkel Y, Onar MK, Sunter T. Clinical REM sleep behavior disorder and motor subtypes in Parkinson's disease: a questionnaire-based study. Clin Neurol Neurosurg 2014; 119: 54-58.
8) Sollinger AB, Goldstein FC, Lah JJ, Levey AI, Factor SA. Mild cognitive impairment in Parkinson's disease: subtypes and motor characteristics. Parkinsonism Relat Disord 2010; 16: 177-180.
9) Reijnders JS, Ehrt U, Lousberg R, Aarsland D, Leentjens AF. The association between motor subtypes and psychopathology in Parkinson's disease. Parkinsonism Relat Disord 2009; 15: 379-382.
10) Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, Huber S, Koller W, Olanow C, Shoulson I. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 1990; 40: 1529-1534.
11) van Rooden SM, Visser M, Verbaan D, Marinus J, van Hilten JJ. Motor patterns in Parkinson's disease: a data-driven approach. Mov Disord 2009; 24: 1042-1047.
12) Herman T, Weiss A, Brozgol M, Wilf-Yarkoni A, Giladi N, Hausdorff JM. Cognitive function and other non-motor features in non-demented Parkinson's disease motor subtypes. J Neural Transm (Vienna) 2015; 122: 1115-1124.
13) Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, Brown RG, Koller W, Barone P, MacPhee G, Kelly L, Rabey M, MacMahon D, Thomas S, Ondo W, Rye D, Forbes A, Tluk S, Dhawan V, Bowron A, Williams AJ, Olanow CW. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMS Quest study. Mov Disord 2006; 21: 916-923.

14) Duncan GW, Khoo TK, Yarnall AJ, O'Brien JT, Coleman SY, Brooks DJ, Barker RA, Burn DJ. Health-related quality of life in early Parkinson's disease: the impact of nonmotor symptoms. Mov Disord 2014; 29: 195-202.

15) Ba F, Obaid M, Wieler M, Camicioli R, Martin WR. Parkinson disease: the relationship between non-motor symptoms and motor phenotype. Can J Neurol Sci 2016; 43: 261-267.

16) Crosiers D, Pickut B, Theuns J, Paul De Deyn P, Van Broeckhoven C, Martinez-Martin P, Chaudhuri KR, Cras P. Non-motor symptoms in a Flanders-Belgian population of 215 Parkinson's disease patients as assessed by the Non-Motor Symptoms Questionnaire. Am J Neurodegener Dis 2012; 1: 160-167.

17) Kompoliti K, Wang QE, Goetz CG, Leurgans S, Raman R. Effects of central dopaminergic stimulation by apomorphine on speech in Parkinson's disease. Neurology 2000; 54: 458-462.

18) de Lau LM, Verbaan D, van Rooden SM, Marinus J, van Hilten JJ. Relation of clinical subtypes in Parkinson's disease with survival. Mov Disord 2014; 29: 150-151.

19) Hyacinthe C, Barraud Q, Tison F, Bezard E, Ghorayeb I. D1 receptor agonist improves sleep-wake parameters in experimental parkinsonism. Neurobiol Dis 2014; 63: 20-24.

20) Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol 2009; 8: 464-474.

21) Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, Hametner EM, Poewe W, Rascol O, Goetz CG, Sampaio C. The movement disorder society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease. Mov Disord 2011; 26 Suppl 3: S42-80.