Parkinsonism and Related Disorders 69 (2019) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Predictors of Pisa syndrome in Chinese patients with Parkinson's disease: A prospective study

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A R T I C L E I N F O

Keywords:
Parkinson's disease
Pisa syndrome
Rapid eye movement sleep behavior disorder
Axial symptoms

A B S T R A C T

Introduction: Pisa Syndrome (PS) is a disabling complication in Parkinson's disease (PD) with unclear pathogenesis, yet studies on the longitudinal observation of PS are absent. This study aims to investigate the clinical predictors of PS from a cohort of Chinese PD patients.

Methods: A total of 373 PD patients without PS were prospectively monitored for approximately 2.5 years. Demographic and clinical data were investigated. A penalized logistic regression model was conducted to discriminate the predictive factors of PS.

Results: Overall, PS was observed in 22 patients (5.9%) during the study period. At baseline, the following variables including Unified PD Rating Scale (UPDRS) part III score, the axial subscore of UPDRS part III, the modified Hoehn and Yahr (H&Y) stage, the subscore "taste or smell" of the Non-Motor Symptoms Scale (NMSS), proportion of males and rapid eye movement sleep behavior disorder (RBD), were significantly higher in patients with PS compared to those without PS ($p < 0.05$). The multivariable penalized logistic regression model indicated that the presence of RBD (OR = 4.088, $p = 0.003$) and higher axial subscore of UPDRS part III (OR = 1.196, $p = 0.002$) predicted a higher risk of developing PS.

Conclusion: PD patients with RBD and more severe axial symptoms are more likely to develop PS in the future.

1. Introduction

Pisa Syndrome (PS) is a postural deformity defined as a marked lateral trunk flexion for at least 10°, which can be aggravated by standing, sitting or walking and completely alleviated by passive mobilization or supine position [1].

PS was first reported in 2003 among patients with Parkinson's disease (PD) [2]. It is a disabling symptom which increases the probability of low back pain, falls, fractures and significantly affects the quality of life of PD patients [3,4]. However, the pathogenesis of PS remains unclear and the treatment of PS in PD is challenging in clinical practice, so early identification of patients who are more prone to developing PS is particularly important.

It is reported that the prevalence of PS in PD patients ranged from 1.9% [5] to 16.5% [6]. Although several cross-sectional studies on the clinical features of PS have been conducted, which PS was found to be associated with older age, longer disease duration and more severe disease stages [4,6], studies on the longitudinal observation of PS are absent. Therefore, we performed a large sample prospective study to investigate the clinical predictors of PS from a cohort of Chinese PD patients.

2. Patients and methods

A total of 408 PD patients who agreed to be followed up were recruited in this study between December 2013 to December 2015 from the Department of Neurology, West China Hospital, Sichuan University. All participants have provided written informed consent. The study was approved by the Ethics Committee of West China Hospital of Sichuan University. All participants met the United Kingdom PD Society Brain Bank Clinical Diagnostic Criteria for PD. The disease duration of participants with PD was required to be ≤ 5 years. Participants were excluded if they presented with PS, history of spinal/vertebral surgery, myasthenia, or primary dystonia at baseline. All of the participants underwent brain magnetic resonance imaging (MRI) to exclude other causes of parkinsonism and if necessary, some patients also underwent full-length spine radiographs and MRI to rule out spinal problems at baseline and during follow-up visits.

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https://doi.org/10.1016/j.parkreldis.2019.10.010
Received 24 April 2019; Received in revised form 9 October 2019; Accepted 10 October 2019
1353-8020/

All participants were followed up at least once, and the average interval from baseline to the last visit was 2.5 ± 1.1 years. All participants were evaluated by professional neurologists on movement disorders through a face-to-face interview during every visit. When patients showed signs of atypical parkinsonism, researchers would reconsider the patient's diagnosis of PD. Participants were excluded if they presented with atypical parkinsonism or other parkinsonian syndromes during the follow-up visits. Patients were allowed to adjust the treatment regimen during the study.

Demographic and clinical data including age, sex, age of onset, disease duration, education level, family history of PD, hyposmia, falls, freezing of gait, festination, rapid eye movement sleep behavior disorder (RBD), treatment regimen, levodopa equivalent daily dose (LEDD) and motor complications were collected. The LEDD was calculated by the commonly used formula given by Tomlinson CL et al. [7]. Then all participants underwent various detailed clinical assessments. The Unified PD Rating Scale (UPDRS) part III score [8] and the modified Hoehn and Yahr (H&Y) stage [9] were used to evaluate the motor disability. For further analysis, part of the UPDRS part III items reflecting asymmetry of parkinsonian signs was derived as the asymmetry subscore, including tremor at rest in upper and lower extremities, action or postural tremor in hands, rigidity in upper and lower extremities, finger taps, hand movements, rapid alternating movements of hands and leg agility, and was calculated as the total value of the differences between sides of each item [10]. The axial subscore was calculated as the total scores on the items of speech, facial expression, neck rigidity, arising from a chair, posture, gait, postural stability, and body bradykinesia [10]. Cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA) [11] and the Frontal Assessment Battery (FAB) [12]. The Non-Motor Symptoms Scale (NMSS) [13] was used to evaluate the overall severity of non-motor symptoms of PD. Meanwhile, the severity of depression was assessed using the Hamilton Depression Scale (HAMD; 24 items) [14], and the severity of anxiety was evaluated using the Hamilton Anxiety Scale (HAMA) [15]. Furthermore, the presence of RBD was based on the Chinese version of the Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire (RBDSQ) with cut off ≥ 5 [16].

All participants underwent a measurement for the angle of the lateral trunk flexion using a wall goniometer and were classified into two groups (with and without PS) according to the most commonly used criterion for PS [1]. If a participant presented with a lateral trunk flexion of at least 10°, and the flexion can be completely alleviated by passive mobilization or supine positioning, he/she was identified as the presence of PS [1]. In addition, we further documented the time point when patients presented with PS.

At the end of this study, 35 participants were excluded from this study: 8 participants were diagnosed with atypical parkinsonism, 5 participants refused the follow-up visit, 10 participants could not be contacted, and 12 participants had incomplete data. Participants who were lost to follow-up showed similar age and sex distribution compared to those who completed the final visit. We reconfirmed the diagnosis of PD for every remaining participant and a total of 373 patients had complete data and were available to statistical analyses.

3. Statistical analyses

All analyses were performed with the SPSS 21.0 and the STATA 15.1. All tests were two-tailed and the p value < 0.05 was considered significant. Continuous data was presented as mean ± standard deviation and was analyzed by the Student's T test. Categorical data was presented as counts (percentages) and was analyzed by the Chi-square test or the Fisher's exact test. Ranked data (H&Y stage) was presented as the median values (quartile) and was analyzed by the Mann-Whitney U test. Eventually, a forward stepwise binary logistic regression model was performed to investigate the potential predictive factors of PS. Presence or absence of PS was employed as the dependent variable. Sex, age, disease duration, LEDD, use of levodopa, use of dopaminergic agonist, use of selegiline, the axial subscore of UPDRS part III, RBD, FAB score, MoCA total score, HAMD score, HAMA score, NMSS total score, the subscores of "miscellaneous" and "taste or smell" in NMSS were employed as covariables, which were selected according to the results (selection criteria $p < 0.1$) from comparisons between PD patients with and without PS or based on previously reported correlative factors [3,4]. It should be noted that if variables were highly correlated in the correlation analyses (e.g. the axial subscore of UPDRS part III and H&Y stage), the variable with the lower p value was allowed to enter the multivariable logistic model.

In order to validate the regression model, we did a Hosmer and Lemeshow test as the statistical diagnostics. We utilized a penalized logistic regression model [17] as a more conservative method to further improve the robustness of the potential predictors. In the penalized regression model, we include the same covariables and dependent variables as the former regression model.

4. Results

The last follow-up data was collected at a mean of 2.5 ± 1.1 years (1.0–6.2 years) from baseline. Of the total 373 participants, 215 patients (57.6%) had ≥ 2 times of organized follow-up visits with the interval of 12 ± 1 months; 158 patients (42.4%) had only one follow-up visit and the median spacing of visits is 2.1 years (1.0–6.2 years). At the end of the study, 22 PD patients developed PS (5.9%) and the average time of PS onset is 5.8 ± 1.4 years (3.8–8.1 years) after PD onset.

The baseline demographic and clinical characteristics of PD patients are presented in Table 1. At baseline, patients with PS had a significantly higher UPDRS III score, a higher axial subscore of UPDRS part III, a higher H&Y stage, higher percentages of males and RBD, compared to those without PS ($p < 0.05$). No significant differences in the rest of the items were found between the two groups.

Comparisons of baseline cognitive evaluation results between PD patients with and without PS are presented in Table 2. The FAB total score, the MoCA total score, as well as subscores of MoCA were not different between the two groups.

Comparisons of the baseline NMSS evaluation between patients with and without PS are presented in Table 3. At baseline, patients with PS exhibited a significantly higher subscore of "taste or smell" from the NMSS than those without PS ($p < 0.05$). The NMSS total score and the scores of its remaining items were not different between the two groups.

As for the demographic and clinical characteristics of all participants at the last visit in this study, please see Supplementary Tables 1–3 in supplementary files.

The potential predictors of future PS are presented in Table 4. The multivariable logistic regression model indicated that the presence of RBD (OR = 4.481, $p = 0.001$), higher axial subscore of UPDRS part III (OR = 1.209, $p = 0.001$) and higher subscore of "taste or smell" in NMSS (OR = 1.166, $p = 0.031$) predicted a higher risk of developing PS. As for the statistical diagnostics, the p value of the Hosmer and Lemeshow test for this regression model was 0.150, which showed acceptable goodness of fit. The penalized regression model indicated that the presence of RBD (OR = 4.088, $p = 0.003$), higher axial subscore of UPDRS part III (OR = 1.196, $p = 0.002$) predicted a higher risk of developing PS. The subscore of "taste or smell" in NMSS was no longer a predictor of PS.

To clarify the relationship between the predictors of PS and duration of follow-up in the study, first we performed a Spearman's correlation analysis for the variable "axial scores" and the duration of follow-up ($p = 0.287$); then we performed a Mann-Whitney U test for the variable "RBD" and the duration of follow-up ($p = 0.692$); finally we did a linear regression analysis to see whether there was a correlation between the two variables together and the duration of follow-up. In the

Table 1
Baseline demographic and clinical features between PD patients with and without PS.

	Total	With PS	Without PS	Test	*p* value
Number of patients	373	22	351		
Sex (male)	211 (56.6%)	17 (77.3%)	194 (55.3%)	2	0.043[a]
Mean age (years)	59.1 ± 11.4	59.0 ± 15.1	59.1 ± 11.1	1	0.980
Mean age of onset (years)	56.6 ± 11.4	56.7 ± 15.0	56.6 ± 11.2	1	0.963
Education level (years)	10.6 ± 3.7	11.1 ± 4.0	10.5 ± 3.7	1	0.441
Disease duration (years)	2.5 ± 1.1	2.3 ± 1.1	2.5 ± 1.1	1	0.306
Family history	41 (11.0%)	3 (13.6%)	38 (10.8%)	2	0.954
Hyposmia	126 (33.8%)	10 (45.5%)	116 (33.0%)	2	0.233
LEDD, levodopa equivalent daily doses (mg/day)	231.6 ± 211.6	287.5 ± 226.1	228.1 ± 210.5	1	0.202
Use of levodopa	230 (61.7%)	14 (63.6%)	216 (61.5%)	2	0.844
Use of dopaminergic agonist	135 (36.2%)	9 (40.9%)	126 (35.9%)	2	0.635
Use of amantadine	60 (16.1%)	3 (13.6%)	57 (16.2%)	2	0.981
Use of anticholinergic agents	24 (6.4%)	2 (9.1%)	22 (6.3%)	2	0.940
Use of entacapone	9 (2.4%)	0	9 (2.6%)	4	1.000
Use of selegiline	2 (0.5%)	0	2 (0.6%)	4	1.000
UPDRS part III	26.4 ± 11.7	34.7 ± 12.7	25.9 ± 11.4	1	0.001[a]
Asymmetry subscore	4.8 ± 3.3	4.3 ± 3.5	4.8 ± 3.3	1	0.447
Axial subscore	7.3 ± 3.9	10.2 ± 5.2	7.1 ± 3.7	1	< 0.001[a]
H&Y stage	2 (0.5)	2.5 (0.5)	2 (0.5)	3	0.005[a]
Motor complication					
Fluctuation	21 (5.6%)	1 (4.5%)	20 (5.7%)	2	1.000
Dyskinesia	8 (2.1%)	0	8 (2.3%)	4	1.000
Falls	15 (4.0%)	1 (4.5%)	14 (4.0%)	4	0.605
Freezing of gait	54 (14.5%)	3 (13.6%)	51 (14.5%)	2	1.000
Festination	71 (19.0%)	3 (13.6%)	68 (19.4%)	2	0.700
RBD	95 (25.5%)	13 (59.1%)	82 (23.4%)	2	< 0.001[a]
FAB	16.1 ± 2.2	15.6 ± 2.3	16.1 ± 2.2	1	0.319
MoCA	24.6 ± 4.1	23.6 ± 4.3	24.7 ± 4.1	1	0.218
NMSS	35.7 ± 31.6	47.4 ± 40.1	35.0 ± 30.9	1	0.074
HAMD	10.3 ± 8.7	14.6 ± 11.6	10.1 ± 8.5	1	0.083
HAMA	7.8 ± 6.9	11.6 ± 10.1	7.6 ± 6.6	1	0.075

PD, Parkinson's disease; PS, Pisa syndrome; LEDD, levodopa equivalent daily doses; UPDRS, Unified PD Rating Scale; asymmetry subscore, including tremor at rest in upper and lower extremities, action or postural tremor in hands, rigidity in upper and lower extremities, finger taps, hand movements, rapid alternating movements of hands and leg agility of the UPDRS part III items, was calculated as the total value of the differences between sides of each item; axial subscore was calculated as the total scores on the UPDRS part III items of speech, facial expression, neck rigidity, arising from a chair, posture, gait, postural stability, and body bradykinesia; H&Y stage, Hoehn and Yahr stage; RBD, rapid eye movement sleep behavior disorder; FAB, Frontal Assessment Battery; MoCA, Montreal Cognitive Assessment; NMSS, Non-Motor Symptoms Scale; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale.
Test 1: Student's T test.
Test 2: Chi-square test.
Test 3: Mann-Whitney *U* test.
Test 4: Fisher's exact test.
[a] Significant difference.

Table 2
Baseline cognitive assessments between PD patients with and without PS.

	Total	With PS	Without PS	*p* value
FAB	16.1 ± 2.2	15.6 ± 2.3	16.1 ± 2.2	0.319
MoCA	24.6 ± 4.1	23.6 ± 4.3	24.7 ± 4.1	0.218
Visuospatial/executive abilities	3.8 ± 1.3	3.4 ± 1.5	3.8 ± 1.3	0.135
Naming	2.5 ± 0.8	2.5 ± 0.9	2.5 ± 0.8	0.815
Attention	5.5 ± 0.8	5.5 ± 0.8	5.5 ± 0.8	0.894
Language	2.1 ± 0.9	1.9 ± 0.8	2.1 ± 0.9	0.180
Abstraction	1.2 ± 0.8	1.3 ± 0.8	1.2 ± 0.8	0.779
Memory	3.1 ± 1.5	2.6 ± 1.5	3.1 ± 1.5	0.149
Orientation	5.8 ± 0.6	5.9 ± 0.4	5.8 ± 0.6	0.426

PD, Parkinson's disease; PS, Pisa syndrome; FAB, Frontal Assessment Battery; MoCA, Montreal Cognitive Assessment.
p value was calculated from the Student's T test.

linear regression model, duration of follow-up was employed as the dependent variable, and the predictors of interest were employed as covariables. As a result, the *p* value was 0.274 for the model test. Furthermore, the two covariables were not correlated with each other. In conclusion, our tests showed that the potential predictors of PS (RBD and axial scores) were not correlated with the duration of follow-up. Thus, the duration of follow-up did not affect the outcome variables, i.e. predictors of PS.

RBD is predictive of various adverse outcomes among PD patients, so in order to verify that it is RBD per se rather than some other correlated event or co-morbidity that is related to PS, we provided the information of motor worsening in patients with consistent medication states during each visit, specifically, 199 PD patients without PS and 10 PD patients with PS. As the results showed in Supplementary Table 4, the overall UPDRS motor worsening, as well as the axial subscore worsening and the asymmetry subscore worsening were not different between patients with and without PS, which indicated that motor worsening did not affect the development of PS. Furthermore, we tested whether PD patients with or without RBD at baseline had different motor worsening. As the results showed in Supplementary Table 5, the overall UPDRS motor worsening, as well as the axial subscore worsening and the asymmetry subscore worsening were not different between patients with and without RBD at baseline, which indicated that RBD did not affect the speed of motor worsening. In summary, we can infer that it is RBD per se that is related to PS.

5. Discussion

To the best of our knowledge, this is the first prospective study to investigate the predictors of PS in a large cohort of PD patients. We found that patients with RBD and more severe axial symptoms are more

Table 3
Baseline NMSS assessments of PD patients with and without PS.

	Total	With PS	Without PS	*p* value
NMSS total	35.7 ± 31.6	47.4 ± 40.1	35.0 ± 30.9	0.074
D1. Cardiovascular	0.9 ± 2.1	1.0 ± 2.6	0.9 ± 2.1	0.923
1.Light-headedness/ dizziness	0.8 ± 1.9	1.0 ± 2.6	0.8 ± 1.8	0.759
2. Falls because of fainting	0.1 ± 0.6	0	0.1 ± 0.6	0.527
D2. Sleep/Fatigue	7.0 ± 7.6	8.2 ± 6.7	7.0 ± 7.6	0.445
3. Daytime sleepiness	1.4 ± 2.2	1.6 ± 1.7	1.4 ± 2.2	0.583
4. Fatigue	1.9 ± 2.7	1.7 ± 2.1	1.9 ± 2.8	0.773
5. Difficulty falling asleep	2.5 ± 3.6	3.1 ± 3.4	2.5 ± 3.7	0.495
6. Restless legs	1.2 ± 2.7	1.8 ± 3.0	1.2 ± 2.7	0.288
D3. Mood/Apathy	8.4 ± 12.2	11.9 ± 16.5	8.1 ± 11.9	0.167
7. Lost interest in surroundings	1.5 ± 2.4	2.6 ± 3.5	1.4 ± 2.3	0.139
8. Lack of motivation	1.4 ± 2.4	2.4 ± 3.5	1.3 ± 2.3	0.155
9. Feelings of nervousness	1.1 ± 2.2	1.5 ± 2.0	1.1 ± 2.2	0.421
10. Feelings of sadness	2.0 ± 2.7	2.1 ± 2.9	2.0 ± 2.7	0.940
11. Flat mood	1.1 ± 2.4	1.4 ± 2.8	1.1 ± 2.3	0.566
12. Difficulty experiencing pleasure	1.3 ± 2.5	2.0 ± 3.2	1.3 ± 2.5	0.208
D4.Perceptual problems/ Hallucinations	0.4 ± 2.3	0.1 ± 0.4	0.4 ± 2.3	0.602
13. Hallucinations	0.1 ± 1.0	0.1 ± 0.2	0.1 ± 1.0	0.700
14. Delusions	0.1 ± 1.0	0	0.1 ± 1.0	0.551
15. Double vision	0.1 ± 0.7	0.1 ± 0.3	0.1 ± 0.7	0.755
D5. Attention/memory	3.4 ± 4.0	4.0 ± 4.8	3.4 ± 4.0	0.521
16. Concentration	0.6 ± 1.5	0.6 ± 1.2	0.6 ± 1.5	0.926
17. Forget things or events	2.0 ± 2.3	2.3 ± 2.9	1.9 ± 2.2	0.488
18. Forget to do things	0.9 ± 1.6	1.1 ± 1.4	0.8 ± 1.6	0.475
D6. Gastrointestinal	2.7 ± 4.3	3.3 ± 4.3	2.7 ± 4.3	0.493
19. Dribbling saliva	0.5 ± 1.6	0.6 ± 1.4	0.5 ± 1.6	0.940
20. Swallowing	0.3 ± 1.1	0.7 ± 2.0	0.3 ± 1.0	0.316
21. Constipation	1.9 ± 3.2	2.1 ± 3.3	1.9 ± 3.2	0.795
D7. Urinary	4.5 ± 6.9	5.6 ± 7.5	4.5 ± 6.8	0.477
22. Urgency	1.0 ± 2.3	1.1 ± 2.7	1.0 ± 2.3	0.819
23. Frequency	1.2 ± 2.7	1.2 ± 2.7	1.2 ± 2.7	0.987
24. Nocturia	2.3 ± 3.1	3.2 ± 3.3	2.3 ± 3.1	0.154
D8. Sexual dysfunction	3.8 ± 6.4	6.4 ± 11.3	3.7 ± 5.9	0.279
25. Interest in sex	1.9 ± 3.2	3.1 ± 5.7	1.9 ± 2.9	0.327
26. Problems having sex	1.9 ± 3.4	3.3 ± 5.6	1.8 ± 3.2	0.239
D9. Miscellaneous	4.5 ± 5.2	7.0 ± 7.0	4.4 ± 5.1	0.098
27. Pain	1.7 ± 2.8	2.2 ± 3.7	1.7 ± 2.8	0.386
28. Taste or smell	1.3 ± 2.4	2.7 ± 3.3	1.2 ± 2.3	0.043[a]
29. Weight change	0.3 ± 1.2	0.7 ± 1.7	0.3 ± 1.2	0.263
30. Excessive sweating	1.2 ± 2.3	1.3 ± 2.4	1.2 ± 2.3	0.766

NMSS, Non-Motor Symptoms Scale; PD, Parkinson's disease; PS, Pisa syndrome.
p value was calculated from the Student's T test.
[a] Significant difference.

likely to develop PS.

RBD is characterized by the loss of normal REM sleep muscle atonia and motor behaviors related to dream content [18]. RBD has a close relationship with neurodegenerative diseases and increases the risk of developing PD [18]. Prior studies have noted the association between postural disabilities and RBD [19], which PD patients with RBD have a higher chance of presenting postural control impairments. The pedunculopontine nucleus (PPN) is involved in the modulation of REM sleep and the pathogenesis of RBD through connections to the medial prefrontal and anterior cingulate cortices [20]. Notably, PPN also has a close relationship with the control of gait and posture through a direct connection to the cortical motor areas [21], and PPN neural activity directly regulates anticipatory postural adjustments [21]. Furthermore, PS can improve after contralateral or ipsilateral stimulation of the PPN [3]. It can therefore be assumed that there is a common subset of neurodegenerative changes which PS and RBD may share, possibly involving the PPN. Our finding also accords with a neuroimaging study, which showed that PD patients with RBD had damage in a subset of PPN neurons connected with areas related to locomotor and arousal networks, promoting the occurrence of both postural disabilities and sleep disorders [22].

Several studies indicated that dysregulation of both dopamine and other neurotransmitter systems have contributed to the development of PS [3,4]. Meanwhile, a study from our research center also inferred that PD patients with RBD might have more widespread degeneration in the central nervous system and involves not only dopaminergic systems but also nondopaminergic systems [23]. Furthermore, animal studies reported that lesions in the pons dorsal tegmentum and the ventral part of the medulla including multiple brainstem nuclei, such as the PPN, locus coeruleus and raphe nucleus, were responsible for RBD [18]. Interestingly, the locus ceruleus and raphe nucleus, rich in noradrenaline and serotonin neurotransmitter, respectively, were believed to have a role in the pathogenesis of PS [4,24]. Taken together, there is the possibility that RBD and PS in PD share a common pathophysiological pathway in which serotonin and noradrenaline are involved.

Studies have shown that RBD was associated with cognitive decline in PD [25], and PD patients with RBD had poorer performance on cognitive tasks measuring working memory, visual search, mental flexibility, processing speed, cognitive inhibition, word retrieval, delayed recall of verbal information and visuospatial organization, which reflects both fronto-striatal and posterior cortical deficits [25]. In the meantime, posture control depends on cognitive and attentional functions. Similarly, Vitale C et al. found a significant association of PS with altered attention and visuoperceptual functions in PD, suggesting that the occurrence of PS may also be associated with alteration of both frontal-striatal systems and posterior cortical areas [26]. Moreover, the PPN and its projections to subcortical and cortical regions have been related to cognitive impairment in PD [27]. As mentioned earlier, the PPN may play a key role in the occurrence of both PS and RBD. Thus, we can assume that there is an overlap of impaired brain regions between RBD and PS in PD, which further contributes to cognitive decline in PD patients. In this study, cognitive function was only tested through simplified scales like FAB and MoCA, and there was no difference between the two groups of patients. Therefore, we intend to utilize more

Table 4
Multivariable logistic regression and penalized regression analysis of predictors of future PS in PD.

Independent significant covariates	OR_1 (95%CI)	p_1 value	OR_2 (95%CI)	p_2 value
RBD	4.481 (1.808-11.107)	0.001[a]	4.088 (1.632-10.237)	0.003[a]
Axial subscore of UPDRS part III	1.209 (1.082-1.352)	0.001[a]	1.196 (1.067-1.341)	0.002[a]
"taste or smell" in NMSS	1.166 (1.049-1.236)	0.031[a]	1.151 (0.994-1.332)	0.060

PS, Pisa syndrome; PD, Parkinson's disease; RBD, rapid eye movement sleep behavior disorder; UPDRS, Unified PD Rating Scale; NMSS, Non-Motor Symptoms Scale; OR, odds ratio.
p_1 value was calculated from a forward stepwise binary logistic regression model with the presence or absence of PS as the dependent variable, and sex, age, disease duration, LEDD, use of levodopa, use of dopaminergic agonist, use of selegiline, the axial subscore of UPDRS part III, RBD, FAB score, MoCA total score, HAMD score, HAMA score, NMSS total score, the subscores of "miscellaneous" and "taste or smell" in NMSS as covariables.
p_2 value was calculated from a penalized logistic regression model with the same covariables and dependent variables as the former logistic regression model.
[a] Significant difference.

detailed scales of cognition in further studies that will be helpful to clarify this question.

In summary, PD patients with RBD have neurodegenerative changes involving the PPN, a pathophysiological pathway involving the non-dopaminergic system and impaired brain regions such as frontal-striatal systems and posterior cortical areas, which may also contribute to the pathogenesis of PS, so PD patients with RBD are more likely to develop PS.

Compared to patients without PS, patients with PS showed a higher UPDRS part III score and a higher H&Y stage in this study, which were similar to the findings of numerous cross-sectional studies [6,26]. In further analysis, patients with PS manifested a higher axial subscore of UPDRS part III. This indicated that patients with PS had more severe axial symptoms. The multivariable penalized logistic regression confirmed axial symptoms as a potential predictor of future PS. Recently an electromyographic (EMG) study reported a lack of synchronization during tonic postural contraction in para-spinal muscles in the 0–25-Hz band in PD patients with PS, which revealed a lack of inter-muscular coherence of axial muscles and a defective muscular fine-tuning in the axis of PS patients [28]. Such an abnormal coherence in agonists muscles has been associated with bradykinesia in PD [29], which suggested that axial bradykinesia could be a contributing factor to PS. Combined with our findings that more severe axial symptoms can predict the development of PS, we reinforce the hypothesis that PS was on account of the motor dysfunction of axial muscles. Besides, since the rigidity, one of the major manifestations in PD, has been referred to as a common mechanism causing postural abnormalities in PD patients [1]. We can infer that patients with serious axial symptoms are likely to suffer from more prominent rigidity and consequently, abnormal postures such as PS may emerge [30].

There are some limitations that cannot be ignored. First, we used a questionnaire (RBDSQ) to diagnose RBD instead of the objective polysomnography (PSG). Second, the interval between follow-up visits among patients was not strictly restricted. It is worth continuing to follow up the cohort with regular interval in the future. Third, we did not discriminate the predictors of PS in patients with different medication states (“ON” or “OFF”), so the role of drug therapy in the pathogenesis of PS was hard to explain. Forth, the statistical comparison in these two groups may deviate the results since the number of patients with PS was much lower in comparison to the number of patients without PS in this study due to the fact that PS is a rare syndrome.

6. Conclusion

In conclusion, the current study found that PD patients with RBD and more severe axial symptoms are more likely to develop PS in the future.

Declaration of competing interest

The authors declare that there was no conflict of interest.

Acknowledgments

The authors thank the patients and their families for their participation in the study. This study was supported by the National Clinical Research Center for Geriatrics,West China Hospital, Sichuan University (Z2018B08).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.10.010.

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