

Pisa syndrome in Parkinson disease

An observational multicenter Italian study

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**Supplemental data
at Neurology.org**

ABSTRACT

Objective: To estimate the prevalence of Pisa syndrome (PS) in patients with Parkinson disease (PD) and to assess the association between PS and demographic and clinical variables.

Methods: In this multicenter cross-sectional study, consecutive outpatients with PD attending 21 movement disorders Italian tertiary centers were enrolled and underwent standardized clinical evaluation. PS was defined as trunk lateral deviation $\geq 10^\circ$. Patients with PD were compared according to the presence of PS for several demographic and clinical variables.

Results: Among 1,631 enrolled patients with PD, PS was detected in 143 patients (8.8%, 95% confidence interval 7.4%–10.3%). Patients with PS were older, had lower body mass index, longer disease duration, higher disease stages, and poorer quality of life. Falls were more frequent in the PS group as well as occurrence of “veering gait” (i.e., the progressive deviation toward one side when patient walked forward and backward with eyes closed). Patients with PS received higher daily levodopa equivalent daily dose and were more likely to be treated with combination of levodopa and dopamine agonists. Osteoporosis and arthrosis were significantly the most frequent associated medical conditions in patients with PS. Multiple explanatory variable logistic regression models confirmed the association of PS with the following variables: Hoehn and Yahr stage, ongoing combined treatment with levodopa and dopamine agonist, associated medical conditions, and presence of veering gait.

Conclusions: Our results suggest that PS is a relatively frequent and often disabling complication in PD, especially in the advanced disease stages. The association is dependent on a number of potentially relevant demographic and clinical variables. *Neurology*® 2015;85:1–11

GLOSSARY

CI = confidence interval; DA = dopamine agonist; H&Y = Hoehn and Yahr; LEDD = levodopa equivalent daily dose; OR = odds ratio; PD = Parkinson disease; PDQ-8 = Parkinson's Disease Questionnaire-8; PS = Pisa syndrome; UPDRS = Unified Parkinson's Disease Rating Scale.

Ekbom et al.¹ first described Pisa syndrome (PS) as a truncal dystonia or pleurothotonus, occurring as a side effect of antipsychotic treatment.^{2,3} The term PS was subsequently applied to patients with dementia and other neurodegenerative diseases who developed lateral trunk

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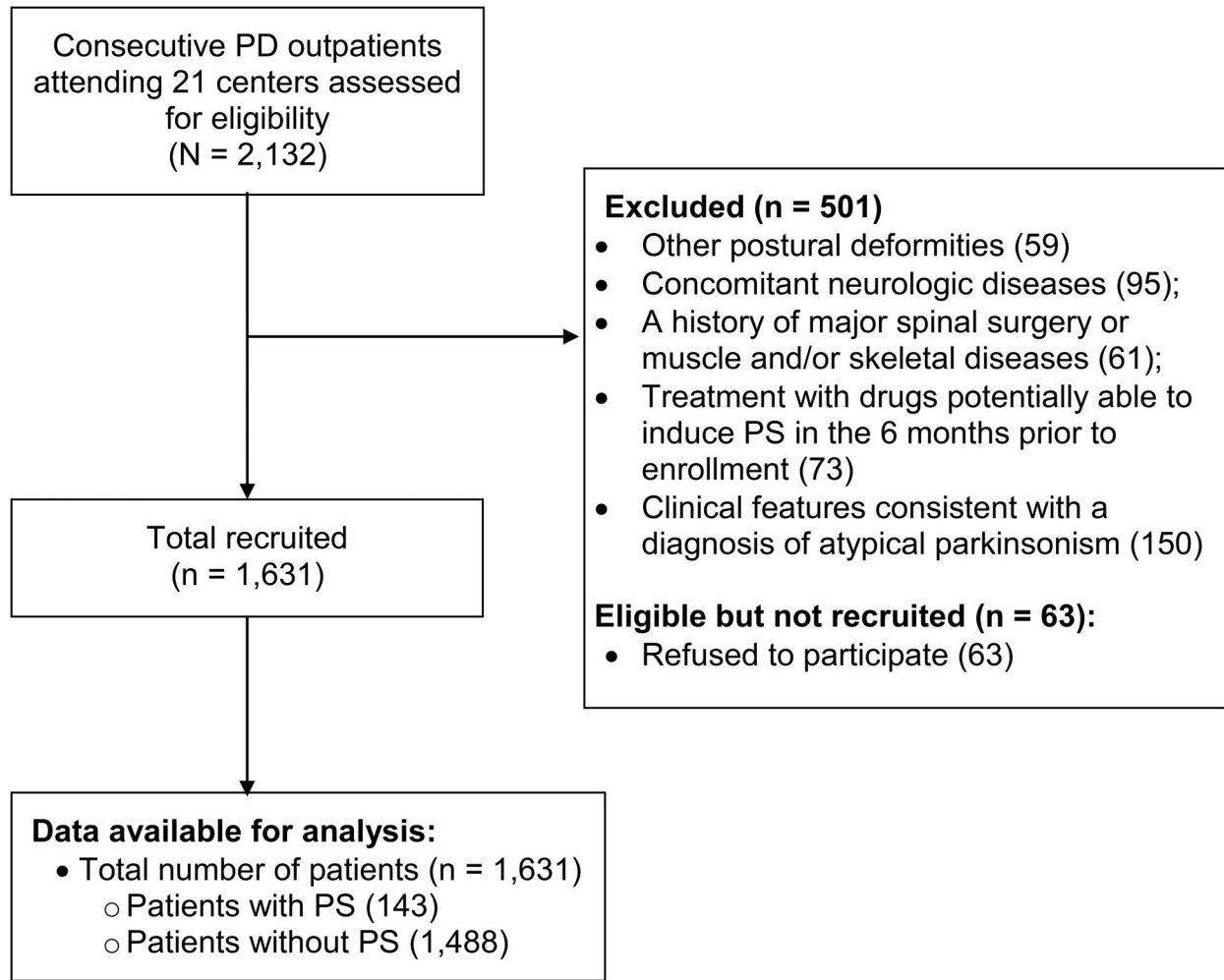
flexion without exposure to neuroleptics.^{4–9} Over the years, it has been associated with antiemetics, antidepressants, central cholinesterase inhibitors, lithium carbonate, and other drugs.¹⁰ More recently, PS has also been reported in patients affected by Parkinson disease (PD) after dopaminergic treatment.^{11–17} Two mutually nonexclusive pathophysiologic hypotheses have been advocated: (1) a central hypothesis, supported by both animal studies and clinical findings and related to an imbalance in basal ganglia functioning along with altered sensory-motor integration; and (2) a peripheral hypothesis, referred to as a primary alteration of the musculoskeletal system.^{2,3} The broad variability of PS clinical features renders its classification uncertain and pathophysiologic explanation is still debated. The direction of trunk deviation with respect to the most affected side has been previously investigated with conflicting results.^{12–20} The relationship between drug exposure and occurrence of PS is also uncertain.^{10–17} Finally, no study could detect a relationship with the stage and severity of the disease or systematically assess the prevalence of this condition with the exception of one small study.²¹

The aforementioned case series have produced conflicting results and demographic, disease-related, and treatment-related factors associated with PS have not yet been clarified. Therefore, this multicenter cross-sectional study was designed to systematically investigate the prevalence of PS and its relationship with clinical and demographic features in a large cohort of consecutive patients with PD. These data would be relevant to identify at-risk patients and PS-associated symptoms that may benefit from earlier therapeutic strategies.

METHODS In the present multicenter cross-sectional study, consecutive outpatients with PD attending 21 movement disorders Italian tertiary centers between February 2012 and July 2013 were enrolled and underwent standardized clinical evaluation. Patients identified with PS underwent a supplementary evaluation by means of an ad hoc questionnaire and a specific neurologic examination (figure 1). PD was diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank criteria.²² Exclusion criteria were as follows: (1) occurrence of other postural deformities (in absence of PS) according to established diagnostic criteria (i.e., camptocormia $\geq 45^\circ$, antecollis $\geq 45^\circ$, or retrocollis)²; (2) concomitant neurologic diseases known to negatively affect posture; (3) a history of major spinal surgery or

muscle and/or skeletal diseases; (4) treatment with drugs potentially able to induce PS (neuroleptics other than clozapine or quetiapine and antiemetics with the exception of domperidone) in the 6 months before enrollment; and (5) clinical features consistent with a diagnosis of atypical parkinsonism.²³ In each center, all patients underwent systematic evaluation in a single session by the same neurologist identified before study initiation. Patients were assessed on their usual drug treatment, during the on phase. The following clinical and demographic variables were recorded in a paper case report form: sex, age, age at PD onset, body mass index, disease duration, PD phenotype (rigid-akinetic, tremor-dominant, or mixed type),²⁴ laterality of motor symptoms at PD onset, latency between PD onset and start of antiparkinsonian therapy, and pharmacologic treatment at disease onset and at latest visit. Levodopa equivalent daily dose (LEDD) was calculated according to established criteria.²⁵ We also evaluated occurrence of falls in the previous month,²⁶ comorbidities (heart diseases, malignancies, diabetes, hypertension, mental disorders, obesity, metabolic disorders, cerebrovascular diseases, physical trauma), associated medical conditions (osteoporosis, arthrosis, rheumatic diseases, otovestibular disorders), and quality of life by means of Parkinson's Disease Questionnaire-8 (PDQ-8).²⁷ Unified Parkinson's Disease Rating Scale (UPDRS), Parts I–IV, was used to assess disease severity.²⁸ Clinical asymmetry was calculated as the differences between the lateralized scores of UPDRS-III items 20–26 of the UPDRS (a difference of ≥ 4 points was considered indicative of motor asymmetry).²⁹ Staging was assessed with the Hoehn and Yahr³⁰ (H&Y) scale. Trunk deviation was measured by means of a wall goniometer and expressed in degrees. Patients were diagnosed with PS when presenting with a lateral flexion of the trunk of at least 10° and it was almost completely reverted by passive mobilization or supine positioning.² According to the angle of the lateral flexion of the trunk, we further divided patients with PS into 2 groups: mild ($< 20^\circ$) and severe ($\geq 20^\circ$) forms (figure e-1 on the *Neurology*[®] Web site at Neurology.org). Patients with PS were further evaluated to exclude co-occurrence of other postural deformities of the sagittal plane such as camptocormia and/or antecollis, fulfilling the available diagnostic criteria.² To disclose possible proprioceptive and vestibular dysfunctions,¹⁷ individuals were tested with a modified version of the stepping test³¹ by asking patients to walk forward and backward with eyes closed: the occurrence of a “veering gait” was defined as the progressive deviation (30° or more) toward one side in 3 consecutive trials of 5 m. The following information was gathered for patients with PS, by means of an ad hoc questionnaire and clinical evaluation: latency to develop PS after PD onset, PS duration, PS direction, and presence of metronome sign (defined as an alternate leaning behavior occurring toward both sides). The pattern of PS onset (< 1 month: acute; ≥ 1 month, < 3 months: subchronic; ≥ 3 months: chronic) and its relationship with drug regimen changes were also recorded. We also investigated the following: awareness of trunk leaning by asking the patients whether they felt tilted on one side, while sitting on a chair with the forearms lying on the legs; occurrence of sensory trick (defined as any motor act able to transiently improve posture not due to a mechanical effect); and presence of head compensation (defined as head deviation away from the bending side to preserve a horizontal vision). Chronic dorsal or lumbar pain intensity was ascertained and graded on a visual analog scale graded from 0 (no pain at all) to 10 (excruciating

Figure 1 Study design: Flowchart illustrating how patients with PD and PS were selected from the whole study population



PD = Parkinson disease; PS = Pisa syndrome.

pain).³² Finally, patients with PS underwent a spine x-ray in a static upright standing position to further disclose orthopedic conditions potentially leading to lateral bending of the trunk.

Standard protocol approvals, registrations, and patient consents. The study was approved by the institutional review boards of the participating centers. All patients were informed about the nature of the study and gave their consent to participate in the study.

Sample size. Sample size was estimated to be between 1,000 and 1,800 patients and was calculated considering different binomial 95% confidence intervals (CIs) for the a priori estimation of PS of 2% based on previous studies,^{19,21} considering a high level of precision (wide 95% CI from 1% to 2%).

Statistical analyses. Missing data were explored. Absolute and relative frequencies were calculated for categorical data and tested by χ^2 tests after checking the minimum acceptable number of expected frequencies (≥ 5). Nonnormality of continuous variables was checked by visual inspection of distribution and confirmed by Kolmogorov–Smirnov tests. Since several continuous variables were not normally distributed, values were expressed as means \pm SDs and compared across groups using nonparametric Mann–Whitney *U* tests. Unadjusted odds ratios (ORs) (95% CIs) between PS and each of the sociodemographic and clinical

characteristics were obtained by estimating a series of univariate logistic regression models with PS as the dependent variable and sociodemographic and clinical features as the independent variables.

Subsequently, adjusted ORs (95% CIs) for all possible confounding effects were obtained by estimating a multiple logistic regression model with all sociodemographic and clinical features as the independent variables. Effect modification was also investigated. Independent variables were chosen according to both exploratory analysis results and clinical relevance. Sensitivity analyses were performed to check for robustness of results. First, variables that were not significantly associated in the univariate models were removed from the multiple model and ORs were compared. Second, the effect of missing values was explored by rerunning the univariate logistic regression models on only the subsample with all complete information and by comparing the new unadjusted ORs with the preceding ones. All tests were bilateral at $p < 0.05$. Statistical analyses were performed using STATA 11.0 (StataCorp LP, College Station, TX).

RESULTS Clinical features of the patients with PD. A total of 1,631 patients with PD met the eligibility criteria and entered into the study. None of the patients

excluded because of the occurrence of other postural disorders had PS (figure 1).

Clinical features of patients with PD and PS. One hundred forty-three patients fulfilled the diagnostic criteria for PS (prevalence 8.8%, 95% CI 7.4%–10.3%). Trunk flexion ranged from 10° to 50°, with an average of 17.0° ± 7.4°. Patients were leaning toward the most or the less affected side at a similar proportion. PS appeared 7 ± 5 years after PD onset with an average duration of 2.6 ± 2.5 years; the majority of patients (69.9%) developed PS in a chronic manner. The remaining clinical characteristics of the patients with PS are provided in table 1. According to the trunk flexion severity, we did not find significant differences between mild and severe PS groups in any of the investigated demographic and clinical variables (table e-1).

Comparison of demographic and clinical features of patients with PD with and without PS. Patients with PS were older, had lower body mass index, a significantly longer disease duration, more severe disease, and worse quality of life compared with patients who did not have PS. Moreover, patients with PS had higher LEDD and were more likely to be treated with a combination of L-dopa and dopamine agonists (DAs). Osteoporosis and arthrosis were significantly more common in patients with PS ($p < 0.001$ and $p < 0.05$, respectively; data not shown). Finally, falls were more likely to occur in the PS group along with veering gait (table 2).

Clinical and demographic variables associated with PS. The univariate logistic regression model yielded a significant association of PS with most of the investigated clinical and demographic features (table 3). After adjusting for all variables in the model, multivariate logistic regression analysis confirmed the above associations with the following variables: H&Y stage (adjusted OR 1.46, 95% CI 1.002–2.13), ongoing antiparkinsonian treatment (L-dopa + DA vs L-dopa monotherapy; adjusted OR 1.93, 95% CI 1.10–3.39), associated medical conditions (adjusted OR 1.66, 95% CI 1.11–2.48), and presence of veering gait (adjusted OR 3.71, 95% CI 2.37–5.81). Considering trunk flexion severity as an independent variable, univariate logistic regression analysis failed to detect a significant association with any of the investigated clinical and demographic features (table e-1); by contrast, the multivariate logistic regression model yielded a significant positive association with H&Y stage (adjusted OR 3.01, 95% CI 1.23–7.34) and comorbidities (adjusted OR 3.16, 95% CI 1.16–8.58), whereas being female decreased the risk of having severe PS by 72% (adjusted OR 0.28, 95% CI 0.09–0.88) (table 4). Missing data

were assessed on the whole sample. The subgroup without PS showed very low percentages on all variables (ranging from 0% to 2.3%), with the exception of UPDRS-III right and left score (10.3%) and clinical asymmetry (9.6%). Sensitivity analyses were performed on univariate logistic regression models and did not show any effect of missing values. The final models were performed on completers.

DISCUSSION In this multicenter cross-sectional study enrolling a large cohort of consecutive patients with PD, PS had a prevalence of 8.8%. Patients with PS were older, had a significantly longer disease duration, more severe disease, and worse quality of life. Moreover, they were more likely to be treated with a combination of L-dopa and DA and had higher daily LEDD. Additional new findings in our study were that patients with PS were more likely to report falls, associated medical conditions, and veering gait.

The only available study to assess the prevalence of PS in a single-center series of patients with PD found a prevalence of 1.9%, although it was designed for therapeutic purposes.²¹ According to a recently proposed criterion,² we defined PS as a lateral flexion of the trunk $\geq 10^\circ$. We did not find any significant difference in clinical and demographic features when we stratified patients with PS in 2 further groups (mild and severe PS) according to severity of lateral bending using a cutoff of 20°. The lack of significant between-group differences suggests that the adopted definition of PS can accurately identify patients as a homogeneous clinical group.

We found that patients with PS had more severe disease by H&Y staging. Multivariate logistic regression confirmed this association, suggesting that patients in more advanced PD stages are more likely to develop PS. Tassorelli et al.²⁰ did not find an association with H&Y in a small sample of patients with PD; nevertheless, they reported that PS was more likely to be found in patients with greater asymmetry subscore, suggesting the possibility that more marked asymmetry of the disease is associated with an increased risk of developing PS. The association of poor quality of life with PS in our cohort supports its clinical effect as motor manifestation of PD; however, this was not confirmed by multivariate logistic regression analysis, suggesting that PS might not be the principal determinant of poor quality of life but other factors associated with longer disease duration are also contributing.

Regarding exposure to dopaminergic drugs, patients with PS were treated with higher LEDD, likely mirroring a more advanced disease stage. Nevertheless, a significant association between PS and concomitant use of L-dopa and DA survived the

Table 1 Clinical features of patients with PD and PS

Variables	Totals	Mean (SD) or n (%)
PS degrees, mean (SD)	143	17 (7.4)
Latency of PS after PD onset, mean (SD), y	143	7 (5)
PS duration, mean (SD), y	143	2.6 (2.5)
PS direction, n (%)	143	
Right		99 (69.2)
Left		44 (30.8)
Side of PD symptoms at onset and PS inclination, n (%)	143	
Ipsilateral		58 (40.5)
Contralateral		59 (41.3)
Bilateral onset		26 (18.2)
PS pattern of onset, n (%)	143	
<1 mo (acute)		19 (13.3)
≥1 mo and <3 mo (subchronic)		24 (16.8)
≥3 mo (chronic)		100 (69.9)
PS development after drug modification, n (%)	143	
Yes		21 (14.7)
No		122 (85.3)
PS awareness, n (%)	143	
Yes		119 (83.2)
No		24 (16.8)
Back pain, n (%)	143	
Yes		101 (70.6)
No		42 (29.4)
VAS pain, mean (SD)	101	6 (2.3)
Metronome PS, n (%)	134	
Yes		13 (9.7)
No		121 (90.3)
Head compensation, n (%)	138	
Yes		59 (42.7)
No		79 (57.3)
Sensory trick, n (%)	143	
Yes		24 (16.8)
No		119 (83.2)

Abbreviations: PD = Parkinson disease; PS = Pisa syndrome; VAS = visual analog scale.

multivariate logistic regression analysis. This association deserves future studies because DAs have been previously associated with the development of both PS and antecollis.² PS developed after drug regimen changes in almost 15% of patients, whereas no correlation to drug exposure or treatment modification was observed in the remaining patients, regardless of the pattern of occurrence. PS might arise from an increase and/or decrease of dopamine agents.^{11–18} It has been proposed that interactions between dopamine and nondopaminergic neurotransmitters are

implicated in drug-induced PS.^{10,17} Dopamine exposure might act as a priming factor leading to an imbalance at the striatal level with an increased response in the sensitized, more denervated striatum and promoting PS occurrence in some predisposed persons.^{3,17} However, our data partly contrast with the imbalance hypothesis because we did not confirm previous studies showing that patients with PS lean away from their dominant PD side.^{12,16–20} Indeed, in cases with a clear motor asymmetry, trunk flexion was contralateral or ipsilateral with a ratio close to 1:1. This suggests that unbalance of basal ganglia output is not the only pathophysiologic mechanism to explain PS occurrence and points to the possible contribution of different mechanisms.

Finally, a transient improvement of PS following a “sensory trick” was also reported by a small number of patients, suggesting a dystonic etiology of such condition. Although clinical observations and EMG findings support the dystonic hypothesis, electrophysiologic studies have found contradictory patterns of EMG activity and are not conclusive.^{19–21,33} This is in keeping with the hypothesis that dystonia may be an early and transient phenomenon. As the postural deformity becomes structured, the dystonic component might disappear with secondary musculoskeletal changes being prevalent.^{2,3,34} Accordingly, co-occurrence of moderate to severe lower back pain was reported by 70.6% of patients with PS. Pain might arise from alteration of the musculoskeletal system as a protective mechanism to prevent joint excursion.² Co-occurrence of associated medical conditions such as osteoporosis and arthrosis with lower body mass index may further increase the risk of developing abnormal posture as documented in our PS series. Once again, as disease progresses, pathologic changes and fibrosis of soft tissues would in turn promote the transition from compensatory-reversible to structured abnormal posture.^{2,3,34}

Although patients with PS can have impaired perception of their vertical position,^{2,3,18} the majority of patients in our series were aware of their leaning posture; however, only half adopted a head compensation to correct the alignment of the visual inflow. Co-occurrence of back pain might have further contributed to emphasize their perception of postural verticality by focusing attention on body image. The clinical observation of patients with PS deviating from a straight line when walking blindfolded (veering gait) might be attributable to the unmasking of an unbalanced vestibular tone resulting from labyrinthine dysfunction. Indeed, an impaired processing of vestibular information has been associated with PS occurrence in patients with PD.^{3,17,35} In the absence of vestibular testing, we cannot rule out the possibility that mechanical factors destabilizing

Table 2 Comparison of the demographic and clinical features of patients with PD with and without Pisa syndrome*

	All patients	With Pisa syndrome	Without Pisa syndrome	p Value [†]
No. of patients	1,631	143	1,488	
Sex, n (%)				0.49
Male	936 (58.0)	79 (55.2)	857 (58.2) ^a	
Female	679 (42.0)	64 (44.8)	615 (41.8) ^a	
Age, mean (SD), y	69.0 (9.6)	71.1 (8.0)	68.8 (9.7) ^a	<0.05 [‡]
Body mass index, mean (SD)	26.2 (4.2)	25.5 (3.9)	26.3 (4.3) ^b	<0.05 [‡]
Age at PD onset, mean (SD), y	61.4 (10.4)	61.1 (9.8)	61.5 (10.5) ^c	0.51
Disease duration, mean (SD), y	7.1 (4.9)	9.6 (5.3)	6.9 (4.8) ^d	<0.0001 [‡]
H&Y stage, mean (SD)	2.1 (0.7)	2.6 (0.8)	2.1 (0.7) ^e	<0.0001 [‡]
H&Y stage, n (%)				<0.0001 [‡]
0-1§	212 (13.1)	6 (4.2)	206 (14.0)	
1.5	145 (9.0)	9 (6.3)	136 (9.2)	
2	671 (41.5)	39 (27.3)	632 (42.9)	
2.5	307 (19.0)	29 (20.3)	278 (18.9)	
3	216 (13.4)	41 (28.7)	175 (11.9)	
4-5¶	65 (4.0)	19 (13.3)	46 (3.1)	
UPDRS score during the on state, mean (SD)				
I	2.5 (2.5)	3 (2.7)	2.5 (2.5) ^a	<0.01 [‡]
II	9.7 (7.3)	13.2 (8)	9.4 (7.2) ^f	<0.0001 [‡]
III	22.1 (11.2)	27.9 (10.4)	21.6 (11.1) ^g	<0.0001 [‡]
III, right	7.9 (4.9)	9.2 (4.5)	7.8 (5) ^h	<0.001 [‡]
III, left	7.5 (5.1)	9.3 (4.7)	7.3 (5.1) ⁱ	<0.0001 [‡]
IV	2.5 (3.2)	3.5 (3.7)	2.3 (3.1) ^j	<0.0001 [‡]
Dominant phenotype, n (%)				0.11
Tremor type	753 (46.6)	55 (38.5)	698 (47.4) ^a	
Bradykinetic/rigid type	607 (37.6)	60 (41.9)	547 (37.2) ^a	
Mixed type	255 (15.8)	28 (19.6)	227 (15.4) ^a	
Laterality of PD symptom onset, n (%)				0.09
Right	785 (48.5)	58 (40.5)	727 (49.3) ^k	
Left	611 (37.8)	59 (41.3)	552 (37.5) ^k	
Bilateral	221 (13.7)	26 (18.2)	195 (13.2) ^k	
Clinical asymmetry, n (%)				0.18
Yes	862 (58.4)	76 (53.2)	786 (59.0) ^l	
No	613 (41.6)	67 (46.8)	546 (41.0) ^l	
PDQ-8, mean (SD)	8.2 (6.1)	10.1 (5.8)	8.1 (6.1) ^m	<0.0001 [‡]
Latency between PD onset and drug introduction, mean (SD), y	1.3 (2.0)	1.5 (2.8)	1.3 (2) ^d	0.19
First pharmacologic therapy, n (%)				0.34
L-Dopa monotherapy	589 (36.2)	57 (39.8)	532 (35.9) ⁿ	
DA monotherapy	608 (37.4)	54 (37.8)	554 (37.4) ⁿ	
L-Dopa + DA	126 (7.8)	13 (9.1)	113 (7.6) ⁿ	
Other antiparkinsonian drugs	303 (18.6)	19 (13.3)	284 (19.1) ⁿ	

Continued

Table 2 Continued

	All patients	With Pisa syndrome	Without Pisa syndrome	p Value [†]
Ongoing pharmacologic therapy, n (%)				<0.01 [‡]
L-Dopa monotherapy	370 (22.7)	24 (16.8)	346 (23.3) [Ⓟ]	
DA monotherapy	92 (5.7)	3 (2.1)	89 (6.0) [Ⓟ]	
L-Dopa + DA	488 (30.0)	59 (41.3)	429 (28.9) [Ⓟ]	
Other antiparkinsonian drugs	678 (41.6)	57 (39.8)	621 (41.8) [Ⓟ]	
L-Dopa equivalent daily dose, mean (SD), mg	424.9 (307.0)	570.4 (272.6)	410.7 (306.6) [Ⓟ]	<0.0001 [‡]
Comorbidities, n (%)				0.38
Yes	1,169 (71.7)	98 (68.5)	1,071 (72.0)	
No	462 (28.3)	45 (31.5)	417 (28.0)	
Associated medical conditions, n (%)				<0.0001 [‡]
Yes	617 (37.8)	78 (54.5)	539 (36.2)	
No	1,014 (62.2)	65 (45.5)	949 (63.8)	
Falls, n (%)				<0.0001 [‡]
Yes	173 (10.6)	28 (19.6)	145 (9.7)	
No	1,458 (89.4)	115 (80.4)	1,343 (90.3)	
Veering gait, n (%)				<0.0001 [‡]
Yes	193 (11.8)	43 (30.1)	150 (10.1)	
No	1,438 (88.2)	100 (69.9)	1,338 (89.9)	

Abbreviations: DA = dopamine agonist; H&Y = Hoehn and Yahr; PD = Parkinson disease; PDQ-8 = Parkinson's Disease Questionnaire-8; UPDRS = Unified Parkinson's Disease Rating Scale.

L-Dopa = L-dopa + carbidopa, L-dopa + carbidopa extended release, L-dopa + benserazide, L-dopa + benserazide extended release, melevodopa + carbidopa. DA = pramipexole, pramipexole extended release, ropinirole, ropinirole extended release, rotigotine, pergolide, cabergoline, apomorphine. Other antiparkinsonian drugs = anticholinergics, MAO-B inhibitors, amantadine, tolcapone.

* n = 1,631. Without Pisa syndrome total cases are reported as follows, with missing values in parentheses: a = 1,472 (16); b = 1,451 (37); c = 1,470 (18); d = 1,486 (2); e = 1,473 (15); f = 1,484 (4); g = 1,485 (3); h = 1,321 (167); i = 1,320 (168); j = 1,466 (22); k = 1,474 (14); l = 1,332 (156); m = 1,478 (10); n = 1,483 (5); o = 1,464 (24).

[†]Nonparametric Mann-Whitney U test for continuous variables; χ^2 for categorical variables.

[‡]Significant.

[Ⓟ]Three cases in stage 0 added to stage 1.

[¶]Nine cases in stage 5 added to stage 4.

patients while walking might have contributed to the occurrence of veering gait in our patients with PS.

Finally, patients with PS were more likely to report falls. This confirms previous studies showing that postural abnormalities are associated with increased risk of falling, along with a fall history, greater disease severity, and longer disease duration.^{36,37} However, this might point toward an involvement of brainstem structures that have a role in the physiology of axial control, as already hypothesized for camptocormia, which has been linked to oculomotor³⁸ and sleep³⁹ impairment as well as atrophic changes of the axial surface of the midbrain.⁴⁰

The present study may have several limitations. We excluded other postural abnormalities not combined with PS. Although the co-occurrence of mixed deformities has been investigated in our cohort, we did not find any patients who fulfilled the available

diagnostic criteria for camptocormia ($\geq 45^\circ$) or other rarer postural disorders such as antecollis ($\geq 45^\circ$) or retrocollis.² This might have been caused by our sample size, not enough powered to detect the association with rare phenomena, or by the service-based nature of our cohort carrying the risk of selection bias, which might have led to excluding patients with more severe trunk abnormalities who were unable to attend the outpatient clinic. Moreover, we did not include healthy age-matched controls or patients with PS that arose from other causes. As additional limitations, we defined PS as a lateral flexion $\geq 10^\circ$, although no consistent diagnostic criteria of PS are available. Because of the cross-sectional design of our study and the lack of laboratory tests, we could not accurately determine the timing of PS onset or the efficacy of the treatment, and we could not speculate on the pathophysiologic mechanisms underpinning PS in PD. We also recognize that for some of the features

Table 3 Clinical and demographic variables associated with PS

Independent variable	Total sample	Unadjusted			Adjusted ^a		
		OR	95% CI	p Value	OR	95% CI	p Value
No. of patients	1,631						
Sex, females vs males	1,615	1.13	0.80-1.60	0.49	0.98	0.65-1.47	0.91
Age, y	1,615	1.03	1.01-1.05	<0.01 ^b	0.62	0.32-1.23	0.17
BMI	1,594	0.95	0.91-0.996	<0.05 ^b	0.97	0.93-1.02	0.26
Age at PD onset, y	1,613	0.99	0.98-1.01	0.67	1.62	0.82-3.19	0.17
Disease duration, y	1,629	1.09	1.06-1.13	<0.001 ^b	1.71	0.86-3.37	0.13
H&Y stage	1,616	2.34	1.87-2.92	<0.001 ^b	1.46	1.002-2.13	0.049 ^b
UPDRS during the on state							
I	1,616	1.09	1.02-1.15	<0.01 ^b	0.98	0.90-1.07	0.69
II	1,627	1.06	1.04-1.08	<0.001 ^b	1.02	0.98-1.06	0.42
III	1,628	1.05	1.03-1.06	<0.001 ^b	1.03	0.99-1.07	0.14
III, right	1,464	1.05	1.02-1.09	<0.01 ^b	0.98	0.92-1.04	0.46
III, left	1,463	1.07	1.04-1.11	<0.001 ^b	0.98	0.92-1.04	0.43
IV	1,609	1.10	1.05-1.15	<0.001 ^b	0.96	0.89-1.03	0.23
Dominant phenotype							
Bradykinetic/rigid type vs tremor type		1.39	0.95-2.04	0.09	1.18	0.76-1.85	0.46
Mixed type vs tremor type		1.57	0.97-2.53	0.07	1.10	0.63-1.91	0.74
Laterality of PD symptom onset							
Left vs right	1,617	1.34	0.92-1.96	0.13	1.26	0.76-2.09	0.37
Right and left vs right		1.67	1.02-2.72	<0.05 ^b	1.47	0.81-2.68	0.20
Clinical asymmetry, yes vs no	1,475	0.79	0.56-1.11	0.18	0.94	0.64-1.39	0.76
PDQ-8	1,621	1.05	1.03-1.08	<0.001 ^b	0.99	0.95-1.03	0.57
Latency between PD symptom onset and drug introduction, y	1,629	1.04	0.97-1.11	0.27	0.99	0.92-1.06	0.72
First pharmacologic therapy							
DA monotherapy vs L-dopa monotherapy	1,626	0.91	0.62-1.34	0.64	1.19	0.75-1.88	0.46
L-Dopa + DA vs L-dopa monotherapy		1.07	0.57-2.03	0.83	1.15	0.57-2.35	0.70
Other antiparkinsonian drugs vs L-dopa monotherapy		0.62	0.36-1.07	0.09	0.84	0.45-1.56	0.58
Ongoing pharmacologic therapy							
DA monotherapy vs L-dopa monotherapy	1,628	0.49	0.14-1.65	0.25	1.22	0.32-4.65	0.77
L-Dopa + DA vs L-dopa monotherapy		1.98	1.21-3.25	<0.01 ^b	1.93	1.10-3.39	<0.05 ^b
Other antiparkinsonian drugs vs L-dopa monotherapy		1.32	0.81-2.17	0.27	1.52	0.85-2.72	0.16
L-Dopa equivalent daily dose, mg	1,607	1.08	1.05-1.11	<0.001 ^b	1.03	0.99-1.07	0.11
Comorbidities, yes vs no	1,631	0.85	0.59-1.23	0.38	0.85	0.56-1.30	0.45
Associated medical conditions, yes vs no	1,631	2.11	1.50-2.99	<0.001 ^b	1.66	1.11-2.48	<0.05 ^b
Falls, yes vs no	1,631	2.26	1.44-3.53	<0.001 ^b	1.24	0.71-2.15	0.45
Veering gait, yes vs no	1,631	3.84	2.58-5.70	<0.001 ^b	3.71	2.37-5.81	<0.001 ^b

Abbreviations: BMI = body mass index; CI = confidence interval; DA = dopamine agonist; H&Y = Hoehn and Yahr; OR = odds ratio; PD = Parkinson disease; PDQ-8 = Parkinson's Disease Questionnaire-8; PS = Pisa syndrome; UPDRS = Unified Parkinson's Disease Rating Scale.

L-Dopa = L-dopa + carbidopa, L-dopa + carbidopa extended release, L-dopa + benserazide, L-dopa + benserazide extended release, melevodopa + carbidopa. DA = pramipexole, pramipexole extended release, ropinirole, ropinirole extended release, rotigotine, pergolide, cabergoline, apomorphine. Other antiparkinsonian drugs = anticholinergics, MAO-B inhibitors, amantadine, tolcapone.

^an = 1,306.

^bSignificant associations at p < 0.05.

collected in our population, there is a lack of validated scales; e.g., the awareness of vertical position was discerned solely from a single question regarding the

subjective perception of body orientation while sitting. Finally, because of the large study sample included, we were unable to perform cognitive

Table 4 Comparison of the demographic and clinical characteristics between patients with mild and severe trunk flexion^a

Independent variable	Adjusted ^a		
	OR	95% CI	p Value
Sex, females vs males	0.28	0.09-0.88	<0.05 ^b
Age, y	0.98	0.93-1.04	0.57
BMI	0.95	0.84-1.07	0.39
Disease duration of PD, y	0.93	0.84-1.03	0.15
H&Y stage	3.01	1.23-7.34	<0.05 ^b
UPDRS score during the on state			
I	0.83	0.66-1.03	0.09
II	0.95	0.87-1.03	0.22
III	1.05	0.99-1.11	0.10
IV	1.14	0.97-1.34	0.11
Dominant phenotype			
Bradykinetic/rigid type vs tremor type	0.93	0.33-2.67	0.89
Mixed type vs tremor type	1.42	0.42-4.78	0.58
Laterality of PD symptom onset			
Left vs right	1.51	0.59-3.85	0.39
Right and left vs right	0.23	0.52-1.04	0.056
Clinical asymmetry, yes vs no	1.08	0.42-2.77	0.87
PDQ-8	0.97	0.88-1.07	0.056
Latency between PD symptom onset and drug introduction, y	0.71	0.50-1.00	0.050
First pharmacologic therapy			
DA monotherapy vs L-dopa monotherapy	1.33	0.45-3.96	0.61
L-Dopa + DA vs L-dopa monotherapy	2.52	0.49-12.9	0.27
Other antiparkinsonian drugs vs L-dopa monotherapy	4.13	0.97-17.6	0.055
Ongoing pharmacologic therapy			
DA monotherapy vs L-dopa monotherapy	0.57	0.02-17.2	0.74
L-Dopa + DA vs L-dopa monotherapy	2.75	0.63-11.9	0.18
Other antiparkinsonian drugs vs L-dopa monotherapy	2.39	0.53-10.8	0.26
L-Dopa equivalent daily dose, mg/d	0.96	0.87-1.06	0.40
Comorbidities, yes vs no	3.16	1.16-8.58	<0.05 ^b
Associated medical conditions, yes vs no	0.86	0.32-2.32	0.77
Falls, yes vs no	0.41	0.10-1.66	0.21
Veering gait, yes vs no	1.59	0.61-4.15	0.35

Abbreviations: BMI = body mass index; CI = confidence interval; DA = dopamine agonist; H&Y = Hoehn and Yahr; OR = odds ratio; PD = Parkinson disease; PDQ-8 = Parkinson's Disease Questionnaire-8; UPDRS = Unified Parkinson's Disease Rating Scale.

Variables age at onset of PD and UPDRS-III score during the on state right and left not included because of collinearity. L-Dopa = L-dopa + carbidopa, L-dopa + carbidopa extended release, L-dopa + benserazide, L-dopa + benserazide extended release, melevodopa + carbidopa. DA = pramipexole, pramipexole extended release, ropinirole, ropinirole extended release, rotigotine, pergolide, cabergoline, apomorphine. Other antiparkinsonian drugs = anticholinergics, MAO-B inhibitors, amantadine, tolcapone.

^a n = 143.

^b Significant associations at p < 0.05.

assessment or evaluate whether patients with cognitive impairment were more likely to develop PS.

Despite the aforementioned limitations, our findings indicate that PS is a relatively common postural alteration in patients with PD, and is associated with

more severe PD. Moreover, combination of L-dopa and DA along with gait and balance abnormalities, disease progression, and concomitant medical conditions (arthrosis and osteoporosis) may be independent risk factors for PS development. Our findings would

be relevant for designing studies with the aim of understanding the pathophysiologic mechanisms of PS in PD and identifying at-risk patients who may benefit from tailored therapeutic strategies. Early detection and treatment of PS may prevent fixed, irreversible deformities, thereby avoiding complications that may arise from such a disabling condition.

AUTHOR CONTRIBUTIONS

Michele Tinazzi: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision. Alfonso Fasano: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, study supervision. Christian Geroin: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision. Francesca Morgante: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Roberto Ceravolo: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval. Simone Rossi: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Astrid Thomas: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Giovanni Fabbrini: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data. Annarita Bentivoglio: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Filippo Tamma: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data. Giovanni Cossu: study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data. Nicola Modugno: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Mario Zappia: study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Maria Antonietta Volontè: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Carlo Dallochio: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients. Giovanni Abbruzzese: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data. Claudio Pacchetti: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, study supervision. Roberto Marconi: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Giovanni Defazio: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Margherita Canesi: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Antonino Cannas: study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Antonio Pisani: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data, study supervision. Rina Mirandola: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis. Paolo Barone: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and

will give final approval, acquisition of data. Carmine Vitale: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data.

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