

Pisa Syndrome in Parkinson's Disease: Clinical, Electromyographic, and Radiological Characterization

Cristina Tassorelli, MD, PhD,^{1,3*} Anna Furnari, MD,² Simona Buscone, MD,¹ Enrico Alfonsi, MD,¹ Claudio Pacchetti, MD,¹ Roberta Zangaglia, MD,¹ Anna Pichiecchio, MD,¹ Stefano Bastianello, MD,¹ Alessandro Lozza, MD,¹ Marta Allena, MD,¹ Monica Bolla, MD,¹ Giorgio Sandrini, MD,^{1,3} Giuseppe Nappi, MD,¹ and Emilia Martignoni, MD⁴

¹IRCCS "National Neurological Institute C. Mondino" Foundation, Pavia, Italy

²IRCCS Centro Neurolesi "Bonino-Pulejo," Messina, Italy

³Department of Public Health and Neurosciences, University of Pavia, Pavia, Italy

⁴Unit of Neurorehabilitation and Movement Disorders, IRCCS S. Maugeri Foundation, Scientific Institute of Tradate and Department of Medical Sciences, University of Insubria, Varese, Italy

ABSTRACT: Abnormal postures of the trunk are a typical feature of Parkinson's disease (PD). These include Pisa syndrome (PS), a tonic lateral flexion of the trunk associated with slight rotation along the sagittal plane. In this study we describe clinical, electromyographic (EMG), and radiological features of PS in a group of 20 PD patients. All patients with trunk deviation underwent EMG and radiological (RX and CT scan) investigation. Clinical characteristics of patients with PS were compared with a control group of PD patients without trunk deviation. PD patients with PS showed a significantly higher score of disease asymmetry compared with the control group. In the majority of patients with PS, trunk bending was contralateral to the side of symptom onset. EMG showed abnormal tonic hyperac-

tivity on the side of the deviation in the paravertebral thoracic muscles and in the abdominal oblique muscles. CT of the lumbar paraspinal muscles showed muscular atrophy more marked on the side of the deviation, with a craniocaudal gradient. PS may represent a complication of advanced PD in a subgroup of patients who show more marked asymmetry of disease and who have detectable hyperactivity of the dorsal paravertebral muscles on the less affected side. This postural abnormality deserves attention and proper early treatment to prevent comorbidities and pain. © 2011 Movement Disorder Society

Key Words: dystonia; Parkinson; neuroimaging; pain; scoliosis

Abnormal posture of the trunk is a typical feature of extrapyramidal disorders,¹⁻⁴ particularly Parkinson's disease (PD). Camptocormia,⁵⁻⁷ scoliosis,¹⁻³ lateral

flexion,⁸ and anterocollis⁹⁻¹¹ have all been described in PD and other parkinsonisms.^{1,3,12-14}

The sustained lateral bending of the trunk, associated or not with rotation of the spine along the sagittal plane, is often referred to as Pisa syndrome (PS). PS¹⁵ was originally described by Ekblom (1972) in patients on psychiatric drugs. The term was subsequently applied to patients with Alzheimer's disease with and without neuroleptic exposure, in subjects with Lewy body dementia,^{16,17} and in patients on antiemetics and cholinesterase inhibitors.^{18,19}

Lateral trunk flexion has also been reported in idiopathic PD patients²⁰⁻²⁴ in the absence of treatment with antipsychotics, antiemetics, or cholinesterase inhibitors.

Some authors consider lateral trunk flexion in PD and levodopa-responding parkinsonism as a truncal

*Correspondence to: Cristina Tassorelli, IRCCS National Neurological Institute C. Mondino Foundation, Via Mondino 2, 27100 Pavia, Italy; cristina.tassorelli@mondino.it

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TABLE 1. General characteristics of patients (group 1, Parkinson's disease with trunk deviation) and controls (group 2, Parkinson's disease without trunk deviation)*

Variable	Group 1, trunk deviation (n = 20)	Group 2, no trunk deviation (n = 21)	Significance
Age (y)	71.4 ± 6.1	71.1 ± 6.7	Ns
Disease duration (y)	9.9 ± 3.3	9.2 ± 4.1	Ns
Sex: M/W	10/10	9/12	Ns
Symptoms at clinical onset	Akinetic-rigid in 10 patients, complete phenotype in 10 patients	Akinetic-rigid in 10 patients, complete phenotype in 11 patients	Ns
UPDRS-III score	31.7 ± 9.9	34.0 ± 13.3	Ns
Functional Independence Measure	105.1 ± 15.7	100.0 ± 23.1	Ns
Hoehn & Yahr stage	9 patients with stage II 10 patients with stage III 1 patient with stage IV	10 patients with stage II 10 patients with stage III 1 patient with stage IV	Ns
Treatment	L alone: 4 L + DA: 7 L + DA + COMTi: 3 Any combination of L, DA, and/or COMTi + quetiapine: 6	L alone: 8 L + DA: 5 L + COMTi: 3 Any combination of L, DA, and/or COMTi + quetiapine: 5	Ns
Freezing	6	8	Ns
Hallucinations	7	5	Ns
Motor fluctuations	16	15	Ns
Dorsal-lumbar pain	17 patients (85%)	10 patients (47.6%)	.03
Intensity of dorsal-lumbar pain	7.1 ± 1.3	4.5 ± 1.1	.02

Data are expressed as mean ± standard deviation.

M, men; W, women; L, levodopa; DA, dopamine agonists; COMTi, COMT inhibitors; UPDRS-III, Unified Parkinson's Disease Rating Scale motor subscale.

dystonia, although electromyographic (EMG) recordings yielded contradictory results.^{24,25}

In this study we describe the clinical, electromyographic, and radiological patterns of PS in a representative group (n = 20) of patients with idiopathic PD who presented with lateral flexion of the trunk associated with axial rotation along the sagittal plane in order to provide a more comprehensive description of the clinical and instrumental characteristics of PS in PD patients.

Patients and Methods

Patients

Over a 2-year period (from October 2005 to September 2007), around 300 consecutive patients fulfilling the UK Brain Bank criteria for idiopathic Parkinson's disease²⁶ were seen in our Neurorehabilitation Department. Of these, we selected 55 patients with a clinically detectable scoliosis (at least 15 degrees on a wall goniometer). Twenty of these 55 subjects were excluded from the study because of:

- actual or previous use of anticholinesterase inhibitors or typical neuroleptics;
- positive history of spinal surgery or spinal trauma or idiopathic scoliosis;
- presence of autonomic failure, evidence of poor response to levodopa, and presence of cerebellar syndrome (according to the criteria for probable

multiple system atrophy [MSA] defined by Gilman et al²⁷);

- presence of at least 1 of the following red flags for MSA: early instability, rapid progression, bulbar dysfunction, respiratory dysfunction, or emotional incontinence.²⁸

The remaining 35 patients underwent spine radiogram in the standing position, and among them, we recruited 20 consecutive patients who:

- had a Cobb's angle greater than 11 degrees²⁹ (identified as the cut-off value for clinically relevant scoliosis); and
- did not have vertebral bone fractures.

These 20 subjects with idiopathic PD and PS formed group 1. The control group (group 2) was formed by 21 consecutive PD patients without any clinical or radiological evidence of lateral deviation of the trunk, randomly selected from the population of the 300 consecutive PD patients. The patients in group 2 were age-, sex-, and stage-matched with those in group 1. All participants gave their written informed consent to participate in the study, which was approved by the ethics committee of the IRCCS "National Neurological Institute C. Mondino" Foundation (Pavia, Italy). Table 1 shows the general characteristics of the 2 groups.

Clinical Evaluation

In addition to the clinical characteristics reported in Table 1, in group 1 the following variables were collected:

- latency from onset of clinical symptoms to start of levodopa therapy (to test the hypothesis that lateral inclination of the trunk might be related to a delay in starting levodopa therapy);
- duration of disease and latency to development of PS;
- direction of the deviation;
- pattern of onset of deviation. In this regard, given the absence of precise criteria in the literature, the following were adopted arbitrarily: acute onset when the deviation developed within 4 weeks, subchronic onset when it developed over 6 months, and chronic onset when it developed over more than 6 months;
- presence of axial rotation;
- presence/absence of dorsal or lumbar pain on a daily basis, together with its intensity graded on a visual analog scale graded from 0 (no pain at all) to 10 (excruciating pain).

The patients were clinically evaluated by a neurologist with expertise in movement disorders (C.T., G.S., R.Z., or C.P.) who filled in the Unified Parkinson's Disease Rating Scale motor subscale (UPDRS-III).³⁰ The clinical evaluation also included accurate testing of muscle mass, strength, and range of motion.

For analytical purposes, the UPDRS-III score was divided into 2 subscores: axial subscore and asymmetry subscore. The axial subscore was the sum of the scores on the items relating to speech, facial expression, neck rigidity, rising from a chair, posture, gait, postural stability, and body hypokinesia. The asymmetry subscore was calculated as the mean value of the differences between sides of the items regarding tremor at rest in hands and feet, action tremor in hands, rigidity in arms and legs, finger taps, hand movements, rapid alternating movements, and leg agility. The Functional Independence Measure scale, as an indicator of functional autonomy,³¹ was administered to each patient by the same trained neurologist (C.T.).

Instrumental Investigations

Instrumental investigation was performed only in patients from group 1 and consisted of:

1. X-ray of the spine for calculating Cobb's angle according to Cobb's method³²;
2. Computerized tomography (CT) scan of the dorsolumbar spinal muscles;
3. EMG and electrokinesigraphic analysis of thoracic paraspinal T7–T10 and abdominal oblique muscles of both sides;
4. Movement analysis.

Patients also underwent clinical biochemistry investigations for serum creatinine kinase, lactate dehydrogenase, aldolase, myoglobin, C-reactive protein, sedimentation rate, phosphate and calcium, thyroid function, and immunological (antinuclear antibodies) tests, all of which showed results within normal limits.

EMG

We performed both conventional EMG investigation and electrokinesigraphic analysis of thoracic T7–10 and abdominal oblique muscles of both sides. The thoracic level of paraspinal muscles was selected based on preliminary EMG recordings in lumbar paraspinal muscles of these patients, which yielded contradictory results in terms of neurogenic pattern (6 patients), myogenic pattern (4 subjects), and noninterpretable pattern (10 subjects). Furthermore, activation of the lumbar muscles on the concave side at the lumbar level was not recordable in many of the PD patients with PS. An electromyograph Synergy SYN5-C (Viasys Healthcare, Manor Way, Old Woking, Surrey, UK) was used.

Conventional EMG investigation with quantitative motor unit action potential (MUAP) analysis of 20 motor units for each muscle was performed by inserting a coaxial needle electrode in T6–T7 paravertebral thoracic muscles and abdominal oblique muscles of both sides. EMG signals were filtered between 3 Hz and 2 kHz to evaluate rest activity and MUAP amplitude and duration parameters. MUAP amplitude and duration of the patients were compared with our laboratory reference values obtained by EMG testing of 35 normal subjects (age range, 25–78 years; mean age, 57 years). Electrokinesigraphic investigation was made by applying 2 monopolar needle electrodes (Ambu A/S Ballerup-DK-Neuroline twisted pair subdermal; 12 × 0.40 mm) into the muscle at a distance of 30 mm between active and indifferent electrodes. EMG signals for electrokinesigraphic examination were rectified and band-pass-filtered between 100 Hz and 2 kHz.

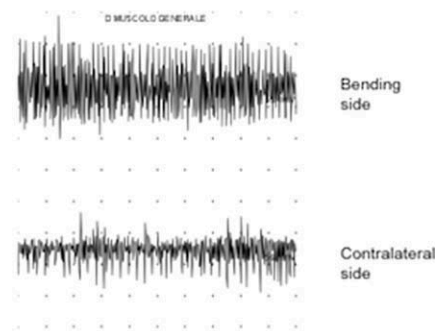
Imaging

We performed conventional radiographic investigation of the spine with the patients in the upright position in the anterior-posterior and lateral projections. CT scans of the lumbar portion of the spine were performed with patients lying in the supine position.

Atrophy severity was graded according to the degree of fatty degeneration as mild (+) when only traces of increased signal intensity could be observed in otherwise well-preserved muscle, moderate (++) when less than 50% of the muscle showed increased signal intensity, or severe (+++) when at least 50% of the muscle showed increased signal intensity.^{33,34}



FIG. 1. Representative example of a PD patient with Pisa syndrome leaning on the right side. At the clinical evaluation, dorsal and lumbar paraspinal muscles seemed hypertrophic on the left side, whereas they were hardly palpable on the right side. EMG at the T10 level disclosed hyperactivity on the bending side. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Movement Analysis

Computerized motion analysis of the spine was performed in the upright standing posture (ELITE, BTS Engineering, Milan, Italy) with a sampling rate of 100 Hz (see ref. 35 for more details).

Results

Clinical Data

All the PD patients with PS showed lateral inclination of the spine associated with axial rotation, which was frequently contralateral to the side of the deviation, although in a few cases it was ipsilateral (Fig. 1). The mean lateral inclination was of 22.9 ± 5.1 degrees, whereas the mean axial rotation along the spine was 11.6 ± 3.3 degrees.

No significant differences were observed between groups 1 and 2 in general characteristics of the disease (Table 1). No between-group differences were observed in the UPDRS-III axial subscore (group 1, 14.3 ± 7.4 ; group 2, 16.1 ± 3.4). However, analysis of the asymmetry subscore revealed significantly greater asymmetry in group 1 than in group 2 (ANOVA, 0.019; $F = 1.939$). Post hoc *t* test analysis showed that the greater asymmetry observed in group 1 derived from the following items: leg rigidity, finger taps, hand movements, rapid alternating movements, and leg agility (Table 2).

Seventeen of 20 patients (85%) in group 1 reported dorsal or lumbar pain, whereas only 10 of the 21

patients in group 2 (47.6%) complained of pain ($P < .03$, chi-square test). The reported pain intensity was 7.1 ± 1.3 in group 1 and 4.5 ± 1.1 in group 2 ($P < .02$).

Patients in group 1 had no access to sensory tricks for reducing a bent or rotated spine.

Analytical Clinical Profile and Characteristics of Trunk Deviation in Group 1

The clinical characteristics and drug treatment of the patients in group 1 are shown in Table 3. In 13 patients bending was contralateral to the side initially affected by PD, and in 5 patients it was ipsilateral, whereas the remaining 2 patients had bilateral symptoms at PD onset. The majority of subjects ($n = 16$) developed PS over a 6-month period (subchronic pattern of evolution), whereas in the other 4 patients, deviation developed in less than 1 month (acute

TABLE 2. Asymmetry subscore as derived from the UPDRS-III items in the 2 groups of patients (see text for further details)

Variable	Group 1	Group 2	<i>P</i> value
Leg rigidity	0.58 ± 0.51	0.24 ± 0.44	.03
Finger taps	0.58 ± 0.51	0.24 ± 0.54	.04
Hand movements	0.37 ± 0.47	0.10 ± 0.30	.04
Rapid alternating movements	0.42 ± 0.49	0.11 ± 0.35	.03
Leg agility	0.42 ± 0.51	0.10 ± 0.30	.01

TABLE 3. Clinical and radiological characteristics of patients from group 1 (Parkinson's disease with trunk deviation) and of their trunk deviation

Patients	Type of symptoms at clinical onset and duration of disease (y)	Duration of disease/latency between PD onset and PS onset (y)	Time of starting treatment with levodopa	Current treatment	Side of symptoms at clinical onset	Direction of deviation	Side on which atrophy was more marked	Distribution of atrophy (side of prevalence and muscles involved)		
								Multifidus muscle	Latissimus dorsi	Iliopsoas
1 (W)	C	11/8	Within first year	LV + DA + MI + N	R	L	L	+++ caudal	+++ caudal	+++ caudal
2 (M)	C	9/7	Within first year	LV + DA	R	L	L	+++ caudal	+++ caudal	+++ caudal
3 (M)	AR	8/7	Within second year	LV	R	L	L	+++ caudal	+++ caudal	+++ caudal
4 (W)	C	13/11	Within first year	LV + DA	R	L	L	+++ caudal	+++ caudal	+++ caudal
5 (W)	C	14/11	Within first year	LV + DA	R	L	L	+++ caudal	+++ caudal	+++ caudal
6 (M)	AR	17/14	Within first year	LV + DA + N	R	L	MF and LD: R IP: L	+++ caudal	+++ caudal	+++ caudal
7 (W)	C	7/6	Within third year	LV + DA	R	L	L	+++ caudal	+++ caudal	+++ caudal
8 (M)	AR	4/3	Within first year	LV + DA	L	L	L	+++ caudal	+++ caudal	+++ caudal
9 (M)	AR	15/11	Within first year	LV + DA	B	R	R	+++ caudal	+++ caudal	+++ caudal
10 (M)	AR	7/6	Within second year	LV + DA + N	L	R	R	+++ caudal	+++ caudal	+++ caudal
11 (W)	AR	9/6	Within first year	LV + DA + N	R	L	Bilateral	+++ caudal	+++ caudal	+++ caudal
12 (M)	C	9/8	Within third year	LV + DA + MI + N	L	L	MF and LD: L IP: Bilateral	+++ caudal	+++ caudal	+++ caudal
13 (M)	C	12/10	Within first year	LV + DA	R	L	L	+++ caudal	+++ caudal	+++ caudal
14 (M)	AR	8/7	Within first year	LV + DA	R	L	Bilateral	+++ caudal	+++ caudal	+++ caudal
15 (W)	C	12/11	Within fourth year	LV + N	R	L	Bilateral	+++ caudal	+++ caudal	+++ caudal
16 (W)	AR	11/10	Within first year	LV + DA + MI	R	R	R	+++ caudal	+++ caudal	+++ caudal
17 (W)	AR	6/4	Within first year	LV + DA + MI	L	R	R	+++ caudal	+++ caudal	+++ caudal
18 (W)	C	8/7	Within second year	LV + DA	B	L	LD: L IP: R	+++ caudal	+++ caudal	+++ caudal
19 (M)	C	11/9	Within first year	LV + DA + MI	R	R	MF and LD: R IP: L	+++ caudal	+++ caudal	+++ caudal
20 (W)	AR	7/6	Within third year	LV + DA + MI + N	R	R	R	+++ caudal	+++ caudal	+++ caudal

M, man; W, woman; AR, akinetic-rigid type; C, complete phenotype; LV, levodopa; DA, dopamine agonist; MI, MAO inhibitor; N, atypical antipsychotic (quetiapine in all cases but 1, who was taking clozapine); R, right; L, left; B, bilateral; MF, multifidus; LD, latissimus dorsi; IP, iliopsoas.
Degree of muscular atrophy: + = only traces of increased signal intensity were observed in an otherwise well-preserved muscle; ++ = less than 50% of the muscle showed increased signal intensity; +++ = at least 50% of the muscle showed increased signal intensity. Cranial level: D10-L3. Caudal level L4-S1.

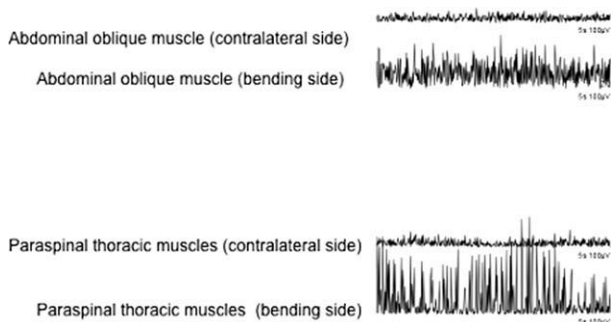


FIG. 2. Representative examples of EMG recordings in the upright position from abdominal oblique muscles and paraspinal thoracic muscles (T7–T8 level) of a PD patient with Pisa syndrome bending on the left side. Persistent tonic EMG activity was observed in both paraspinal thoracic and abdominal oblique muscles of the left side.

pattern of evolution) without any apparent causative factor (falls, pain, etc.).

EMG Findings

Conventional EMG did not show any evidence of spontaneous activity from denervation; both amplitude and duration of MUAP were in the normal range. For paravertebral T7–T10 thoracic muscles, MUAP amplitude range was 200–1345 μV on the right side and 170–1430 μV on the left side, and MUAP duration range was 3.9–9.8 ms on the right side and 4.2–10.0 ms on the left side. For abdominal oblique muscles, MUAP amplitude range was 120–1265 μV on the right side and 110–1290 μV on the left side, and MUAP duration range was 4.5–10.2 ms on the right side and 4.2–11.3 ms on the left side.

Electrokinesiographic investigation with the patient standing in the upright position showed tonic, persis-

tent activity in the abdominal oblique muscle (amplitude range, 550–970 μV) and the paraspinal thoracic muscle (amplitude range, 575–1010 μV) on the bending side, whereas EMG activity was markedly reduced/absent in both muscles on the opposite side (Fig. 2).

Figure 3 shows examples of EMG recordings of paraspinal muscles at the T7–T10 levels in PD patients with PS evaluated first in the upright position and subsequently in the recumbent position. The tonic EMG hyperactivity of paraspinal muscles on the bending side is clearly evident, and it is asymmetrical when compared with the opposite side, where tonic EMG activity was less evident. Tonic activity was present and symmetrical on both sides of PD patients without PS.

Radiological Findings

X-ray of the Spine

Fifteen of the 20 patients showed a c-shaped curve, predominantly characterized by right convexity at the lumbar level (almost two thirds of cases). The s-shaped curve observed in the remaining 5 patients was of the unbalanced type, resulting in deviation toward the left in 4 cases and toward the right in 1 case.

In all patients, lateral deviation of the trunk was associated with axial rotation of the vertebrae along the sagittal plane.

CT Scan of the Paraspinal Muscles in the Dorsolumbar Region

Some degree of muscular atrophy with fatty degeneration was observed in all the patients in group 1 (Table 3). The extent and distribution of muscular

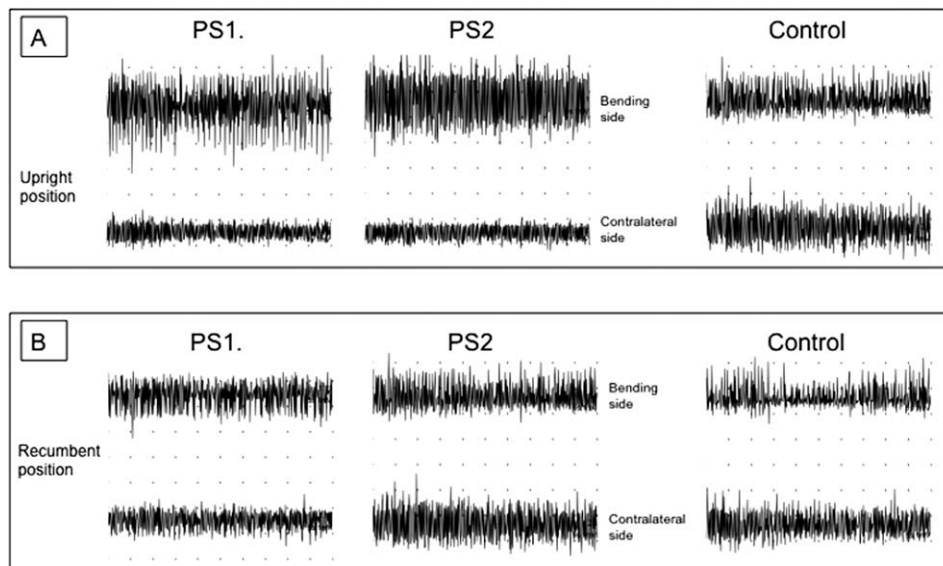


FIG. 3. Representative examples of EMG traces of paraspinal muscles recorded at the T7–T10 levels in 2 PD patients with Pisa syndrome (PS1 and PS2) evaluated first in the upright position (A) and subsequently in the recumbent position (B). The tonic EMG hyperactivity of paraspinal muscles on the bending side was clearly evident and was asymmetrical when compared with the opposite side, where tonic EMG activity was less evident. The EMG traces on the right side show an example of paravertebral muscle activity in a PD patient without PS (control) in both the upright and recumbent positions: tonic activity is present on both sides without any significant asymmetries.

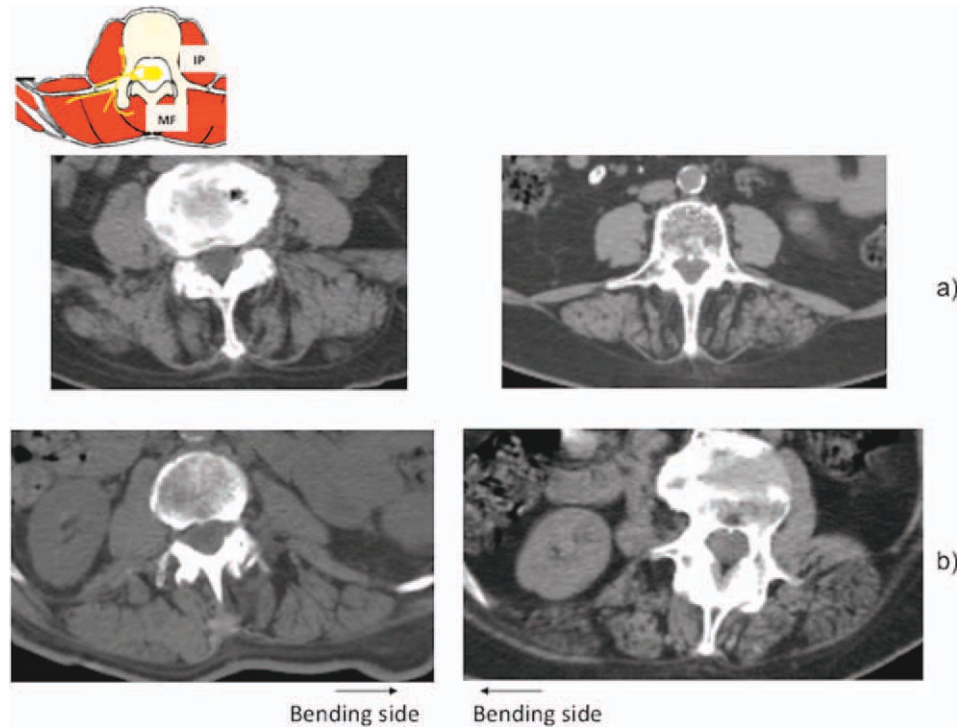


FIG. 4. a: Representative examples of the selective involvement of the multifidus muscle (MF) compared with the ileopsoas (IP). **b:** Representative examples of asymmetrical distribution of atrophy in paravertebral muscles. Note that atrophy is more evident on the bending side. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

atrophy are detailed in Table 3. Atrophy consistently involved the multifidus and latissimus dorsi muscles, especially in their caudal parts (Fig. 4a). With a few exceptions, muscular atrophy was more marked on the concave side (Fig. 4b).

Discussion

We have described PS in 20 patients with PD. The clinical data were compared with a group of PD patients without PS, and they were presented in association with electromyographic and imaging findings.

The first description of lateral deviation of the spine in parkinsonism dates to the beginning of the last century, when Sicard and Alquier³⁶ (1905) reported 8 cases of scoliosis in parkinsonian syndromes. In 1975, Duvoisin and Marsden¹ described lateral flexion in 17 patients with PD and in 4 with postencephalitic parkinsonism. Lateral deviation of the trunk has been reported in isolated cases of idiopathic PD, very occasionally in association with instrumental (neuroimaging or EMG) findings.^{8,20–22} Bonanni et al²⁵ found ipsilateral hyperactivity of the paraspinal muscles on the bending side in a group of 20 subjects suffering from levodopa-responding parkinsonism. However, their findings are hardly comparable to ours because those authors did not clearly state the somatotopic level of EMG exploration. Furthermore, they probably also evaluated MSA subjects, who we theoretically excluded from our group.

Di Matteo et al²⁴ recently investigated EMG features at the T12–L1 level in a group of 10 PD patients with lateral trunk flexion. They found paraspinal muscle hyperactivity more frequently contralateral to the leaning side and, in only a minority of patients, with a typical dystonic pattern. In our paradigm, EMG investigation of paraspinal muscles detected hyperactivity consistently on the side of bending at the thoracic level. At the lumbar level, we obtained contradictory results, which may be explained by the muscle misuse caused by the chronic forced fixed posture of the trunk. This hypothesis was also suggested by the atrophic pattern of muscles at the lumbar level, more marked on the leaning side.

Our clinical findings confirm seminal data¹ that showed how in most PD patients with PS, the direction of trunk deviation is contralateral to the side of the initial clinical symptoms. This feature in our group was also confirmed by x-ray examination.

In the majority of our patients, PS developed over a few months and in a minority of cases even more rapidly (2–3 weeks). The observed rapid onset of PS in the absence of structural bone abnormalities suggests a causative role for the unilateral muscular hyperactivity, possibly dystonic in nature, recorded during the EMG evaluation. This hypothesis also seems supported by the absence of clinical or laboratory signs of acute muscular pathology, in agreement with previous findings.^{37–39} However, along this line of reasoning, it is surprising that neuroimaging of the paraspinal muscles at the lumbar level revealed atrophy limited

to or more prevalent on the bending side. It is noteworthy that none of the patients in our group were evaluated immediately after the onset of PS; therefore, at this stage, it is impossible to ascertain whether muscular atrophy is a consequence of or a causative factor for PS.

Theoretically, trunk deviation in PD may also result from poor symptomatic control of muscular rigidity because of delayed administration of levodopa. However, this explanation seems unlikely because most of our patients began levodopa therapy quite early. In addition, once PS appeared, it did not benefit from further increases in levodopa dosage in any of the patients in whom this option was tried (18 of 20).

The comparison with a group of PD patients without trunk deviation unveiled a significant increase in the asymmetry subscore, which suggests the possibility that more marked asymmetry of the disease is associated with an increased risk of developing PS. Lateral deviation of the trunk in PD is probably linked to central mechanisms. Previous reports suggested that the pathological mechanism underlying this syndrome is related to cholinergic excess, often because of either decreased breakdown of acetylcholine (eg, cholinesterase inhibitors) or decreased dopaminergic inhibition of acetylcholine secondary to dopaminergic antagonism (eg, antipsychotics) or dopaminergic depletion (eg, neurodegenerative disease, PD).^{37,40} The finding that up to 40% of patients with PS show a therapeutic response to anticholinergic therapy supports this theory.³⁸ Peripheral mechanisms may also be involved, although probably in a secondary way, as a consequence of the altered posture.^{39,41}

Taken together with the data from the literature, these findings suggest that PS represents a painful complication of advanced PD in a subgroup of patients with more marked asymmetry of disease.

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