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# Mood and behavioural effects of subthalamic stimulation in Parkinson's disease

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REVIEW

# The Pathogenesis of Pisa Syndrome in Parkinson's Disease

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**ABSTRACT:** Postural abnormalities such as postural deviations affect nearly all patients with advanced Parkinson's disease and represent an important source of disability. Although their existence has long been known, their management remains a challenge as they respond poorly to medication, brain surgery, or physiotherapy. Improving management strategies will require better understanding of the mechanisms underlying such postural deformities.

In this review on the pathophysiology of Pisa syndrome, we examine the data supporting the central and peripheral hypotheses that attempt to explain these lateral trunk deviations. Although the pathophysiology is very probably multifactorial, the bulk of the data supports central, rather than peripheral, hypotheses. The central hypotheses that are best supported by both animal studies and clinical data include asymmetry of basal ganglia output and abnormalities in the central integration of sensory information. Further studies are needed to elucidate the pathophysiology underlying Pisa syndrome. © 2014 International Parkinson and Movement Disorder Society

**Key Words:** Parkinson's disease; postural deviation; basal ganglia; sensory integration; verticality

Abnormal postures are a part of the clinical picture of Parkinson's disease (PD), especially in the advanced stages. Virtually all PD patients develop postural abnormalities in the course of the disease, with severity ranging from mild to severe. The clinical phenotype of abnormal posture is variable. Some patients bend forward, others lean to one side, and in most cases they present with a combination of the two directions of deviation. Lateral deviations of the trunk include Pisa syndrome and scoliosis (Fig. 1).

Unlike most symptoms of PD, which can be satisfactorily controlled by medication, surgery, or physiotherapy, the management of postural deviations remains a challenge. Postural abnormalities have therefore recently attracted increasing attention, because they can represent an important source of disability for patients.[1]

Postural trunk deviations in Parkinson's disease were described by James Parkinson himself.[2] Richer and Meige[3] provided evidence of a typical stooped posture with flexion of the neck, trunk, knees, and elbows (Fig. 2). Sicard and Alquier[4] later observed postural abnormalities of the trunk in 12 of 17 parkinsonian patients, eight of whom were reported to present a so-called scoliosis. Scoliosis has also been described in patients with postencephalitic parkinsonism.[5,6] Although we have known of the existence of these deviations for a long time, no consensus has yet been reached on their definition or diagnostic criteria, and our understanding of their characteristics and underlying causes remains limited.[1]

Lateral deviation in Pisa syndrome may be reducible, especially when the patient lies supine and is free of any mechanical or vertebral restriction. Because of the lack of epidemiological studies in both healthy and

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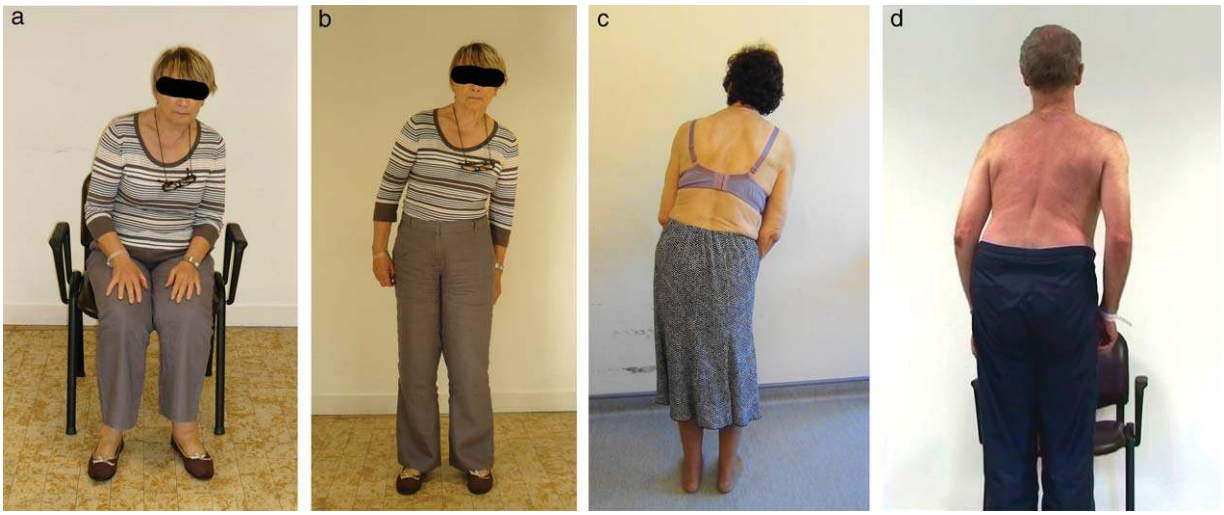


**FIG. 1.** These four pictures represent examples of Pisa syndrome in three patients (**A** and **B,** different views of the same patient; **C** and **D**, other two patients more severely affected).

PD populations, the cutoff between physiological versus pathological lateral inclination of the trunk is somewhat arbitrary. Bonanni et al.[7] suggested a deviation of 15 degrees or more as a diagnostic criterion for Pisa syndrome. More recently, Doherty and colleagues[1] attempted to refine the classification further, to distinguish between Pisa syndrome and scoliosis. They suggested defining Pisa syndrome as being a marked lateral tilt of the trunk (at least 10°), typically reducible (by passive mobilization or when the patient lies down), and scoliosis as being the combination of lateral trunk deviation and vertebral rotation, whose diagnosis requires radiological confirmation.[8] Although this can now be used as a working definition, numerous studies from the last century labeled lateral deviations of the trunk as scoliosis despite the absence of any radiological evaluation.[9]

The lack of consensus on diagnostic criteria and definition contributes to the paucity of epidemiological data and also to the huge difference in reported prevalence, which ranges from 2% to 90%.[7,9-12] Further inconsistencies between studies stem from the inclusion of other parkinsonisms and postencephalitic syndromes in addition to patients with PD.[5-7,9]

The term *Pisa syndrome* was first used to describe the occurrence of lateral trunk deviation in a nonparkinsonian patient treated with neuroleptics.[13] Descriptions of cases resulting from exposure to other drugs such as cholinesterase inhibitors, and in neurodegenerative diseases such as Alzheimer's disease, PD, and multiple system atrophy followed.[14-17] In some cases, the onset of Pisa syndrome was subacute, following a change in antiparkinsonian treatment, such as the introduction of a novel treatment (i.e., rasagiline, dopamine agonists, cholinesterase inhibitor), an increase in dopaminergic treatment dosage, or, on the contrary, the introduction of central dopamine receptor blockers such as antipsychotic agents.[18-22] In some cases, normal posture was recovered on removal of the causative agent.[19] In others, patients were unable to put a date on the onset of the tilting, because they did not initially notice that they were leaning to one side. In such instances, progression is slow, and identification of causative factors is not possible.[23] In our experience, the tilt is sometimes first visible when sitting in this latter category of patient. With time, trunk deviation also persists when standing and walking. At this stage, the curvature may become more complex, with the upper and lower trunk often leaning in opposite directions, as if to compensate for the initial tilt.

The lack of consistent diagnostic criteria in the literature, the paucity of data, and the fact that the data result from retrospective studies or case reports greatly contribute to our poor understanding of the pathophysiological mechanisms. However, both clinical and animal studies have generated a number of hypotheses that can, broadly speaking, be classified into "central" versus "peripheral." Central hypotheses refer to basal ganglia dysfunction and abnormal integration of sensory information. Peripheral hypotheses advocate an alteration of the musculoskeletal system, such as myopathy of the paraspinal muscles. Here, we review the evidence supporting the possible pathophysiological mechanisms underlying Pisa syndrome.

## Central Hypotheses

### Asymmetry of Basal Ganglia Outflow

The key role of the basal ganglia in the pathogenesis of Pisa syndrome is supported by both animal studies and clinical data.

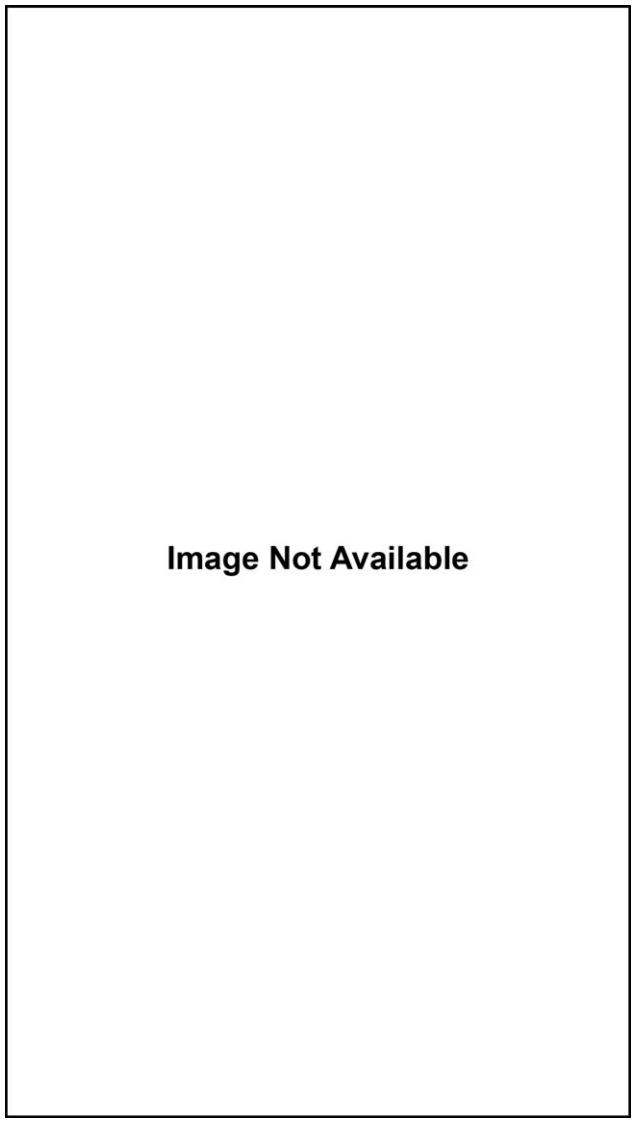


**FIG. 2.** In this statue, Paul Richer shows a 61-year-old woman suffering from Parkinson's disease. Note that the patient is slightly leaning to the left. Reprinted by permission from the Musées Nationaux. At the time this manuscript was accepted and published, "La Parkinsonienne" by Richer was on display at Beaux-arts de Paris, l'école nationale supérieure http://www.ensba.fr/ow2/catzarts/voir.xsp?id=00101-38041&qid=sdx_q3&n=1&e=

### *Animal Models*

Asymmetric functioning of the nigrostriatal dopaminergic projections leading to lateral postural deviations is supported by several animal studies. As early as 1925, Delmas-Marsalet (cited by Martin, 1965[24]) described postural deviation and a persistent tendency to turn in the direction of the lesion in dogs that had undergone unilateral ablation of the head of the caudate nucleus. Conversely, electrical and chemical stimulation (using cholinergic reagents) of this nucleus induced a contralateral rotation. Such observations suggested that the caudate nucleus influences posture and locomotion through striatal cholinergic interneurons, which are under dopaminergic control. Similarly, striatal stimulation has been found to induce contralateral turning in cats.[25-27]

More robust data point to a contribution of lesions of the substantia nigra and the interruption of dopaminergic nigro-striatal projections. Unilateral intrastriatal injections of dopamine and apomorphine (a D1/D2 dopamine agonist) induce asymmetric postures and turning contralateral to the side of injection in intact rats.[28] These effects can be blocked by prior injection of chlorpromazine (a dopaminergic antagonist), whereas unilateral injection of chlorpromazine alone induces ipsilateral turning.[28] Rats with unilateral 6-hydroxydopamine (6-OHDA) nigrostriatal lesions develop axial postural deviations at rest (Fig. 3) and a turning behavior toward the denervated side (i.e., the non-parkinsonian side of the body).[29,30] The greater the dopaminergic denervation, the greater the number of rotations and the more severe the postural deviation.[30] When treated with injections of apomorphine, unilaterally denervated rats switch their turning behavior to the contralateral side.[30] This effect has been attributed to hypersensitization of the denervated dopaminergic receptors, leading to asymmetric dopaminergic stimulation.[31]

Furthermore, postural deviations resulting from 6-OHDA unilateral nigrostriatal lesions have been shown to be reversed and even overcorrected by subthalamic nucleus lesion ipsilateral to the denervated striatum in both rats[32] and marmosets.[33] Finally, in nonparkinsonian primates, unilateral subthalamic nucleus lesion alone can induce postural deviation contralateral to the lesioned side, that is, toward the clinically hypotonic/dyskinetic side.[34]

Animal model studies therefore suggest that asymmetry of dopaminergic activity between the two sides of the basal ganglia loop leads to rotational behavior and postural deviation with curvature toward the more dopamine-depleted striatum, that is, toward the less akineto-rigid hemibody.

### *Clinical Data in PD*

Clinical observations and self-reports of PD patients swimming in circles, deviating from a straight line when crawling on all fours, especially when blindfolded, and stumbling in the direction of the leaning side when walking, in addition to lateral flexion of the trunk, are all reminiscent of animal data.[6,9,35] Swimming in circles was reported by some of our patients as their first motor sign, several years before diagnosis of PD.

Numerous clinical observations support the role of an imbalance in basal ganglia functioning in the pathogenesis of Pisa syndrome. As with the tilting in the direction of the denervated striatum in hemiparkinsonian animal models, most parkinsonian patients with Pisa syndrome tilt toward the less affected side of the body (i.e., toward the more denervated striatum) (Fig. 4), whereas 30% tilt to the other side (Table 1). A recent study confirmed that PD patients with Pisa

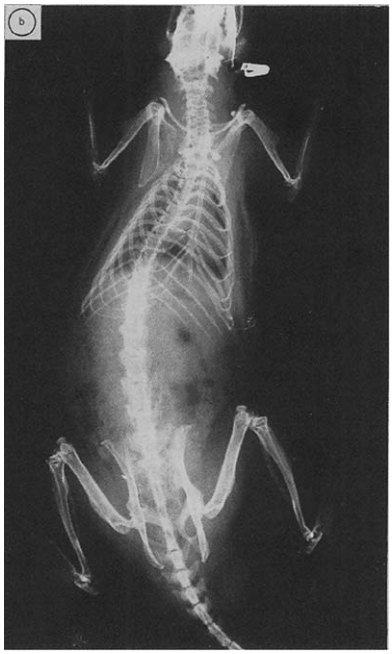

**FIG. 3.** Radiogram of a unilateral right 6-OHDA lesioned rat showing scoliosis toward the denervated side. Reproduced from Herrera-Marschitz M, Utsumi H, Ungerstedt U. J Neurol Neurosurg Psychiatry 1990;53:39-43; with permission of BMJ Publishing Group Ltd.

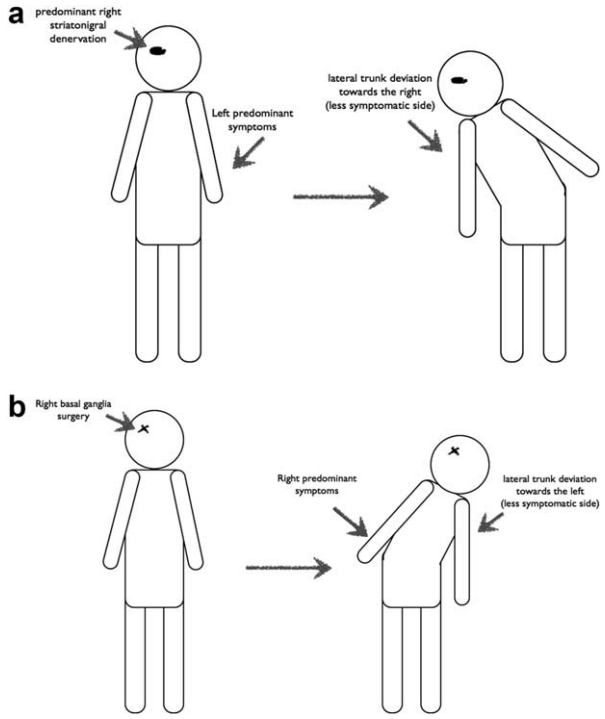


**FIG. 4.** Schematic representation of patients with Parkinson's disease and lateral trunk deviation. (**A**) Patient with a dominant right striatonigral denervation, inducing more severe left-sided symptoms and ultimately a lateral deviation to the right. (**B**) Patient with right-sided basal ganglia surgery (i.e., pallidotomy, subthalamotomy, or thalamotomy) who developed a lateral trunk deviation toward the left (i.e., less affected) side of the body, after surgical treatment.

syndrome present with greater motor symptom asymmetry.[36]

In addition, postural deviations are also seen in patients on whom unilateral pallidotomy, subthalamotomy, or ventrolateral thalamatomy has been performed to alleviate contralateral parkinsonian symptoms.[37-40] In these patients, lateral trunk deviation is directed contralateral to the side of surgery. Therefore, it appears that patients who develop Pisa syndrome after surgical lesion of the basal ganglia lean toward the side of the body less affected by PD (Fig. 4). Interestingly, a second subthalamotomy contralateral to the first surgery, which reduced the asymmetry of parkinsonian signs, also corrected the postural deviation in the two cases described by Su et al.[40]

The involvement of the dopaminergic system in the pathogenesis of Pisa syndrome is supported by the description of its occurrence after neuroleptic, that is, dopaminergic antagonist, exposure.[13,14] Moreover, in PD the introduction, increase, or reduction of dopaminergic medication can induce or reverse Pisa syndrome,[19,23] reinforcing the hypothesis that asymmetry in the functioning of basal ganglia loop might contribute to the development of the syndrome. The addition of a dopaminergic drug might therefore alter the balance between the two striata, leading to a lateral deviation resulting from an increased response in the sensitized, more denervated, striatum, as described in animal models.[29,31]

All patients do not, however, lean toward the less affected side of the body, and some patients present a postural deviation even in the absence of clear symptom asymmetry (Table 1). This suggests that asymmetry of basal ganglia functioning is not the only underlying mechanism. The occurrence of Pisa syndrome as a side effect of cholinesterase inhibitors also points to the contribution of other circuits. Such an effect is not surprising in view of the presence of cholinergic neurons in the striatum and in pontomesencephalic structures, such as the pedunculopontine nucleus (PPN), which are involved in postural control. Interestingly, unilateral PPN stimulation was recently reported to improve Pisa syndrome in one patient.[41] Given the role of the PPN area in postural muscle tone regulation,[42,43] one might hypothesize that any asymmetry or dysregulation in the input to this region might result in asymmetric alteration of the tone of the trunk muscles. Such a mechanism could explain why Pisa syndrome subsides when patients are supine, i.e. when antigravity extensor muscle tone decreases.

In addition to asymmetry in basal ganglia output, mechanisms such as the abnormal integration of sensory information could play a key role in the pathophysiology of Pisa syndrome.

## Abnormal Sensorimotor Integration

### *Vestibular Information*

Although investigation of vestibular function in PD without Pisa syndrome has produced contradictory

**TABLE 1.** Reported direction of lateral trunk deviation in Parkinson's disease

| Study | Pisa Syndrome | Direction of Pisa Syndrome (N.) | | |
|---|---|---|---|---|
| | | Contralateral | Ipsilateral | Uncertain |
| Richer & Meige, 1895[3] | 1 | 1 | - | - |
| Sicard & Alquier, 1905[4] | 8 | 4 | 2 | 2 |
| Onuaguluchi, 1964[5,a] | 5 | 3 | 1 | 1 |
| Martin, 1965[6,a] | 7 | 5 | - | 2 |
| Duvoisin & Marsden, 1975[9,b] | 19 | 16 | 3 | - |
| Grimes et al., 1986[12,c] | 62 | 35 | 27 | - |
| Gambarin et al., 2006[20] | 1 | 1 | - | - |
| Kim et al., 2007[21] | 2 | 1 | 1 | - |
| Cannas et al., 2009[19] | 8 | 1 | 7 | |
| Baik et al., 2009[11] | 32 | 16 | 16 | - |
| Vitale et al., 2011[54] | 11 | 11 | - | - |
| Di Matteo et al., 2011[72,c] | 10 | 7 | 2 | 1 |
| Tassorelli et al., 2012[36,c] | 20 | 13 | 5 | 2 |
| Tinazzi et al., 2013[73] | 13 | 6 | 4 | 3 |
| Total N (%) | 199 | 120 (60.3) | 68 (34.2) | 11 (5.5) |

[a]These studies included post-encephalitic parkinsonism.
[b]It included 17 PD and 4 post-encephalitic parkinsonism.
[c]Side of onset was considered.

results,[44-53] some data have suggested a link between vestibular dysfunction and lateral trunk deviations.

The involvement of the basal ganglia in the processing of vestibular inputs was advocated by Mamo et al.,[38] who observed transient contralateral trunk deviation and contralateral deviation when walking after unilateral subthalamotomy and thalamotomy. Vestibular abnormalities were found in all patients both before and after surgery, irrespective of whether they had initially presented with a postural deviation. The authors concluded that vestibular dysfunction, although necessary, was not sufficient to induce postural abnormalities.

A recent study on PD patients with and without Pisa syndrome focused specifically on the relationship between vestibular function and lateral trunk deviation.[54] Impairment in vestibular function ipsilateral to the leaning side was found in all patients with Pisa syndrome. Interestingly, 4 of 11 patients without Pisa syndrome presented impairments in vestibular function, and two of them later developed ipsilateral Pisa syndrome. Thus, vestibular dysfunction might precede the development of Pisa syndrome, as suggested by Mamo et al.[38]

### Abnormal Spatial Cognition

Maintaining erect posture requires correct body orientation in relation to gravity[55] and relies on the integration of information from visual, vestibular, and somaesthetic sources.[56-59] Impaired sensory integration in PD patients[60-64] could therefore favor an alteration of internal representations of verticality or of the body schema, leading to lateral body deviation. This could explain why parkinsonian patients with moderate Pisa syndrome perceive themselves as standing up straight, and feel as if they are leaning to the contralateral side when corrected.[9,23]

Alterations in perception of postural verticality have been reported in PD patients. Proctor and colleagues[65] assessed 38 PD patients undergoing unilateral thalamotomy before and after surgery. They[65] found abnormal perception of postural verticality in PD, suggesting an alteration in vestibular or proprioceptive integration resulting from basal ganglia disorders. Similarly, Bisdorff et al.[66] found decreased accuracy in the perception of postural verticality in 10 PD patients, compared with a control group. They concluded that patients with PD have decreased sensitivity of their postural orientation. Furukawa (1986) cited by Yokochi[23] described the so-called "oblique sign" in PD patients, that is, their tendency to lean to one side when sitting or lying down. Patients were unaware of this tendency and also presented alterations in postural verticality compared with controls. Such findings lend support to the hypothesis that PD patients with Pisa syndrome have an abnormal perception of their verticality,[23,65,67] and this may contribute to lateral trunk deviation. However, whether such impairment is the cause, or the result, of the syndrome is not clear.

## Peripheral Hypothesis

### Role of the Musculoskeletal System

Although we lack robust data in support of the musculoskeletal hypothesis, some authors have argued that postural abnormalities in PD result from a primary alteration of the musculoskeletal system.[68,69]

The small number of neuropathological studies that have examined this hypothesis were performed on PD patients with camptocormia.[68,70,71] Paraspinal muscle biopsies showed unspecific myopathic changes with type 1 fiber hypertrophy, type 2 fiber loss, loss of oxidative enzyme activity, and myofibrillar disorganization.[68] Similar myopathic changes have been found in patients with tenotomy, suggesting that they could be secondary to altered proprioception in PD and result from, rather than induce, chronic postural deviations.

Unlike camptocormia, to the best of our knowledge, there have been no neuropathological studies on Pisa syndrome. Electromyographic (EMG) recording of paraspinal muscles failed to show any pattern of denervation or myopathy,[36,72,73] except in 2 of 26 patients in one study.[7] Very few imaging studies have been performed on the paraspinal muscles. An early study using lumbar computed tomography scan showed atrophy of the lumbar paraspinal muscles with fatty degeneration, which was more pronounced on the side affected by deviation.[72] More recently, a magnetic resonance imaging study showed bilateral paraspinal lumbar muscle atrophy that was unrelated to the side affected by the deviation, and more pronounced in hypoactive muscles as shown by EMG recordings.[73] Although these data are difficult to interpret, they do not support the notion that musculoskeletal mechanisms play a primary role in Pisa syndrome. Moreover, primary myopathy would also be incompatible with the rapid onset of Pisa syndrome seen after medication changes or surgical treatment for PD. Muscular atrophy is therefore more probably the consequence of chronically altered posture rather than the causative factor, explaining both later-stage worsening and tardive resistance to levodopa.

## Controversy in Phenomenology: Is It Dystonia?

The dystonic hypothesis is based on the analogy with camptocormia, tardive dystonia (the occurrence of a number of cases after neuroleptic exposure), EMG findings of tonic activation of paraspinal muscles ipsilateral to the side affected by deviation, and reports of improvement after botulinum toxin injection.[7] However, EMG findings are not conclusive. Two studies on patients with Pisa syndrome who were standing up found an EMG pattern compatible with dystonia, with continuous activity either in the paraspinal muscles or in the abdominal oblique muscles ipsilateral to the leaning side.[7,36] However, other studies have found contradictory patterns of EMG activity: hyperactivity of paraspinal muscles ipsilateral to the leaning side versus tonic hyperactivity contralateral to the side affected by deviation.[72,73] Methodological issues (muscles examined, recording protocol) make it difficult to compare EMG studies and might account for the discrepancies in the results. In addition, clinical characteristics (disease duration, Pisa syndrome duration, pharmacological treatment) also may influence the pattern of muscle hyperactivity. Tinazzi et al., for example, reported a trend toward a different pattern of muscular atrophy and paraspinal muscle activation depending on the evolution rate of Pisa syndrome.[73] Asymmetry in EMG activity also may be explained by asymmetry in rigidity or could be related to attempts at compensating for the inclination.

The semiology and natural history of Pisa syndrome are often not suggestive of dystonia: the posture is static, neither fixed or mobile; there is no overflow, twisting or twitching, no aggravation with movement, and no sensory tricks. In our experience, patients are often unaware and do not experience pain at the onset of deviation. Early on the deviation is often first visible when sitting and can easily be corrected without inducing any of the features of mobile dystonia. The semiology therefore suggests that sensorimotor integration, rather than the dystonic process, plays a central role. In a recent study, Doherty et al.[74] described how patients with Pisa syndrome, when asked to stand up straight, experienced difficulty in recruiting paraspinal muscles and tended to push down on their knees or to hyperextend their neck.[74] The authors stressed the likely contribution of impaired postural tone and altered proprioception in the genesis of Pisa syndrome, which is congruent with the involvement of basal-ganglia-brainstem cholinergic systems in the onset of the syndrome.

Although the arguments supporting a dystonic mechanism are as yet unconvincing, further studies are needed to rule out this hypothesis.

## Conclusion

The bulk of the data strongly favors the central hypotheses. Both animal and clinical studies support the key role of asymmetric basal ganglia functioning in the pathogenesis of Pisa syndrome. Such asymmetric functioning could lead directly to asymmetric regulation of postural muscle tone through the basal ganglia-brainstem system, and to the altered integration of sensory information. This would in turn induce a misperception of body orientation and the adoption of an asymmetric posture. The installation of a chronic deviation could thus be part of a vicious circle, in which adaptation of sensory processing reinforces the imbalance in basal ganglia output and subsequently the asymmetric posture itself.

Confirmation of the major role played by asymmetry in basal ganglia output and altered sensorimotor integration in the onset of Pisa syndrome could open the way to new therapeutic strategies. ■

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