Pisa syndrome in Parkinson's disease and parkinsonism: clinical features, pathophysiology, and treatment

Paolo Barone, Gabriella Santangelo, Marianna Amboni, Maria Teresa Pellecchia, Carmine Vitale

Pisa syndrome is defined as a reversible lateral bending of the trunk with a tendency to lean to one side. It is a frequent and often disabling complication of Parkinson's disease, and has also been described in several atypical forms of parkinsonism and in neurodegenerative and psychiatric disorders after drug exposure and surgical procedures. Although no consistent diagnostic criteria for Pisa syndrome are available, most investigations have adopted an arbitrary cutoff of at least 10° of lateral flexion for the diagnosis of the syndrome. Pathophysiological mechanisms underlying Pisa syndrome have not been fully explained. One hypothesis emphasises central mechanisms, whereby Pisa syndrome is thought to be caused by alterations in sensory–motor integration pathways; by contrast, a peripheral hypothesis emphasises the role of anatomical changes in the musculoskeletal system. Furthermore, several drugs are reported to induce Pisa syndrome, including antiparkinsonian drugs. As Pisa syndrome might be reversible, clinicians need to be able to recognise this condition early to enable prompt management. Nevertheless, further research is needed to determine optimum treatment strategies.

Lancet Neurol 2016; 15: 1063–74

Neurodegenerative Diseases Centre, Department of Medicine and Surgery, University of Salerno, Salerno, Italy (P Barone MD, M Amboni MD, M T Pellecchia MD)**; Department of Psychology, Second University of Naples, Caserta, Italy** (G Santangelo PhD)**; IDC-Hermitage-Capodimonte, Naples, Italy** (G Santangelo, M Amboni, C Vitale MD)**; and Department of Motor Sciences and Wellness, University Parthenope, Naples, Italy** (C Vitale)

Correspondence to: Carmine Vitale, Department of Motor Sciences and Wellness, University Parthenope, Napoli, Italy
cavit69@hotmail.com

Introduction

Patients with Parkinson's disease or atypical parkinsonism can present with abnormal postures that cause substantial disability and can affect quality of life. Pisa syndrome, defined as a lateral deviation of the spine with a corresponding tendency to lean to one side,[1,2] is one of the most common postural deformities seen in these patients, and lateral flexion of the trunk has been described as "the scoliosis of parkinsonism".[3,4] The term Pisa syndrome was originally used to describe trunk dystonia or pleurothotonus secondary to antipsychotic treatment.[5] Subsequently, the term was applied to patients with dementia,[6–18] parkinsonism,[19–27] and other neurodegenerative diseases[28–32] or neurological disorders including normal pressure hydrocephalus and subdural haematoma[33,34] who developed lateral trunk flexion without exposure to antipsychotic drugs. Additionally, Pisa syndrome has been reported as a primary idiopathic disorder.[35] More recently, Pisa syndrome has been described in patients with Parkinson's disease after modification of dopaminergic treatment or as a complication of surgical procedures for Parkinson's disease management, such as pallidotomy and deep brain stimulation (DBS).[36–47]

Occurrence of postural deformities, in the sagittal or coronal plane or both, have been increasingly recognised as a common complication of Parkinson's disease and have been associated with disease progression and treatment.[1,2] Other common postural abnormities that present in patients with Parkinson's disease and atypical forms of parkinsonism include camptocormia, antecollis, retrocollis, and scoliosis (panel).[1]

In this Review, we focus on Pisa syndrome in the context of both Parkinson's disease and atypical parkinsonism. We provide a detailed update on the definition, epidemiology, and clinical presentation of this postural deformity. We discuss the possible pathophysiological mechanisms underlying Pisa syndrome and emphasise areas in need of further research, and explore the possible treatment options. Because Pisa syndrome is a potentially reversible condition, early recognition and management is crucial to limit the development of structural deformities that can cause severe and irreversible mechanical constraints affecting respiration, mobility, and postural stability.

Definition and epidemiology

The clinical definition of Pisa syndrome is derived mainly from studies of Parkinson's disease rather than atypical parkinsonism. Despite decades of research, there is no consensus on the degree of lateral trunk flexion needed to define Pisa syndrome in Parkinson's disease. In 2007, Bonanni and colleagues[48] defined Pisa syndrome as a lateral flexion of the trunk of more than 15° that increases during walking, is not present when supine, and occurs in the absence of any mechanical restriction to trunk movement, with continuous electromyographic (EMG) activity in the lumbar paraspinal muscles ipsilateral to the bending side. More recently, in 2011, Doherty and colleagues[1] defined Pisa syndrome as a pronounced lateral flexion of greater than 10° while standing, which can be almost completely reversed by passive mobilisation or supine positioning. These authors further differentiate between mobile deformity (Pisa syndrome) and fixed deformity (scoliosis), the latter being diagnosed when there is concomitant lateral trunk flexion and vertebral rotation with a Cobb angle of 10° in the coronal plane.[1,49] Accordingly, radiological confirmation in standing and supine positions is needed for differential diagnosis of Pisa syndrome. The proposed diagnostic criteria of 10 or 15° of lateral trunk flexion might lack sensitivity, as they exclude all patients with flexion of less than 10 or 15°, which could evolve into clinically detectable Pisa syndrome. Nevertheless, by proposing the use of electrophysiological assessment in the diagnosis of Pisa syndrome, Bonanni and colleagues[48] focused mainly on a restricted subset of patients with dystonic features. To

***Panel*: Definitions of postural deformities in Parkinson's disease and parkinsonism**

Camptocormia
Severe flexion (more than 45°) of the thoracolumbar spine in the sagittal plane during standing and walking, almost completely resolving in the recumbent position.

Antecollis
Severe forward flexion (more than 45°) of the head in the sagittal plane, partially overcome by voluntary movement but unable to fully extend the neck against gravity. Rarely seen in Parkinson's disease, it is frequent in multiple system atrophy.

Retrocollis
Abnormal posture of the neck that is held in extension in the sagittal plane. Rare in Parkinson's disease, it is typical of progressive supranuclear palsy.

Scoliosis
Flexion (more than 10°, according to the Cobb method) of the spine in the coronal plane not overcome by voluntary or passive movement, combined with axial rotation of the vertebrae confirmed by radiograph.

overcome such limitations, further validation of diagnostic criteria should be investigated in the context of longitudinal studies with larger study populations.

The absence of a consensus on diagnostic criteria and definition for Pisa syndrome contributes to the inconsistent prevalence rates among studies, ranging from 1·9% to 91%.[1,2,48,50–52] These discrepancies might also be explained by the inclusion of scoliosis as well as Pisa Syndrome and forms of parkinsonism other than Parkinson's disease in some studies, and by the small sample size of most studies.[1–3,5,25,50,51] Two large Italian studies have assessed the prevalence of Pisa syndrome in Parkinson's disease.[48,52] Bonanni and colleagues[48] found a 1·9% prevalence rate in a population of 1400 patients with Parkinson's disease and parkinsonism when using a lateral trunk flexion criteria of 15°. In a multicentre cross-sectional study of 1631 consecutive patients with Parkinson's disease, Tinazzi and colleagues[52] reported a prevalence of Pisa syndrome of 8·8% using the 10° lateral flexion criteria. Conversely, Cervantes and colleagues[53] found no cases of Pisa syndrome or antecollis in a cohort of 416 consecutive patients with Parkinson's disease assessed for musculoskeletal deformities with the clinical criteria proposed by Doherty and colleagues[1] (ie, lateral trunk flexion ≥10° for Pisa syndrome and neck forward flexion ≥45° for antecollis). The absence of Pisa syndrome was interpreted by the authors as the result of milder disease stages in their Parkinson's disease cohort.[53]

Pisa syndrome can occur in patients affected by atypical forms of parkinsonism, especially multiple system atrophy (MSA). The first description of probable Pisa syndrome in a case of pathologically proven striatonigral degeneration—a feature of MSA—was reported in 1978 by Kan,[20] who described a 64-year-old patient who developed "a lumbar scoliosis resulting from muscular dystonia" 2 years after onset of motor symptoms.[20] Two decades later, Colosimo and colleagues[21] reported a second case of Pisa syndrome, with sudden onset, alongside a clinical diagnosis of probable MSA. Postural abnormalities, including severe antecollis and Pisa syndrome, are now recognised as potential indicators of MSA. In a multicentre study from the European MSA Study Group,[24] Pisa syndrome was found in 42% of 57 patients with MSA with a predominant parkinsonian phenotype (both probable and possible according to the first consensus criteria) compared with 2·5% of 116 patients with Parkinson's disease matched for age, sex, and disease duration, reaching a specificity of 97·5% in the differential diagnosis of these disorders.[24] However, the study lacks post-mortem confirmation of MSA or Parkinson's disease diagnosis, and the clinical diagnosis of MSA was the gold standard used to assess the validity of antecollis and Pisa syndrome as warning signs for this disease.

Present evidence suggests that Pisa syndrome is a rare feature of progressive supranuclear palsy (PSP). In a series of 202 consecutive patients with Parkinson's disease, MSA, and PSP assessed for the presence of joint and skeletal deformities, Ashour and colleagues[25] reported camptocormia in 5·3% of patients with PSP compared with 12·2% of patients with Parkinson's disease and 26·3% of patients with MSA, and scoliosis was described in 5·3% of patients with PSP compared with 8·5% of patients with Parkinson's disease and 10·5% of patients with MSA. Ashour and colleagues found no cases of Pisa syndrome in their patient series, although this might be due to the absence of validated diagnostic criteria and the retrospective design of the study. Solla and colleagues[26] described a 69-year-old patient with a diagnosis of probable PSP who presented with a tonic flexion of the trunk of at least 10° to the right that occurred 3 years after the onset of motor symptoms. Furthermore, Noda and colleagues[27] have reported a case of probable PSP with lateral flexion of the trunk, which worsened when the patient was sitting (in a wheelchair) but was alleviated in the supine position.

Clinical features and concomitant medical conditions

Pisa syndrome can develop chronically with subtle onset and gradual progression, or with an acute onset followed by rapid worsening over months.[1,51,52,54] The pattern of onset has been classified according to the time taken to develop clinically definite Pisa syndrome: acute (<1 month), subchronic (≥1 month to <3 months), and chronic (≥3 months). Using these definitions, Tinazzi and colleagues[52] found that most patients in their cohort developed Pisa syndrome chronically. In chronic forms of Pisa syndrome, a slight reversible tilting behaviour