# Axial postural deformities in Parkinson's disease

Thesis submitted in fulfilment of the degree of

Doctor of Medicine (Research)

Reta Lila Weston Institute of Neurological Studies

UCL Institute of Neurology

University College London

2013

Karen M. Doherty

I, Karen M. Doherty confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

Date:

*Abstract*

Studies have been performed to detail the phenomenology, investigate the skeletal changes and explore the spinal biomechanics underlying the main axial deformities – Pisa syndrome and camptocormia in Parkinson's disease.

Results demonstrate that the clinical picture of these deformities varies greatly but that certain particular features allow distinction from other neurological, muscular and bony aetiologies. The tone of the axial muscles, the level at which spinal flexion occurs, the patient's ability and method to try to overcome the chronically abnormal posture, and the flexibility or fixity of the trunk provide clinical pointers to the likely underlying cause. The scoliotic curve in a patient with Pisa syndrome was C-shaped, involved a large element of collapse and occurred without evidence of a secondary upper compensatory curvature (S-shaped curve). On supine imaging patients with camptocormia were severely mechanically disadvantaged as a result of their alordotic lumbar spines in relation to pelvic angulation. This lumbar alordosis may reflect the effects of Parkinson's disease on the axial musculature, particularly in those with axial akinetic rigid predominant PD. Radiological examination also demonstrated that Pisa syndrome was different from de novo degenerative scoliosis and camptocormia not typical of adult onset degenerative kyphosis. Fixed bony changes were rare but the severity of these postural deformities and their consequent effects (e.g. knee flexion contractures, gluteal muscle atrophy) are likely to render conservative interventions unsuccessful unless instigated very early in the evolution of the abnormal posture.

*Papers associated with thesis*

Doherty KM, van de Warrenburg BP, Peralta MC, Silveira-Moriyama L, Azulay JP, Gershanik OS, Bloem BR. 2011. Postural deformities in Parkinson's disease. *Lancet Neurol*, 10(6):538-49.

Doherty KM, Noyce AJ, Silveira-Moriyama L, Nisbet A, Quinn N, Lees AJ. 2012. Familial camptocormia: from dystonia to myopathy. *J Neurol Neurosurg Psychiatry*, 83(3):350-1.

Doherty KM, Silveira-Moriyama L, Giladi N, Bhatia KP, Parton M, Lees AJ. 2012. Camptocormia: don't forget muscle disease in the movement disorder clinic. *J Neurol*, 259(8):1752-4.

Doherty KM, Davagnanam I, Molloy S, Silveira-Moriyama L, Lees AJ. 2013. Pisa syndrome in Parkinson's disease: a mobile or fixed deformity? *J Neurol Neurosurg Psychiatry,* Published Online First: 26 March doi:10.1136/jnnp-2012-304700.

*Other papers published during research period*

Ling H, Braschinsky M, Taba P, Luus SM, Doherty K, Hotter A, Poewe W, Lees AJ. 2011. Decades of delayed diagnosis in 4 levodopa-responsive young-onset monogenetic parkinsonism patients. *Mov Disord*, 26 (7): 1337-1340.

Djamshidian A, O'Sullivan SS, Doherty K, Lees AJ, Averbeck BB. 2011. Altruistic punishment in patients with Parkinson's disease with and without impulsive behaviour. *Neuropsychologia*, 49(1):103-7.

*Ahmed Z, *Doherty KM, Silveira-Moriyama L, Bandopadhyay R, Lashley T, Mamais A, Hondhamuni G, Wray S, Newcombe J, O'Sullivan SS, Wroe S, de Silva R, Holton JL, Lees AJ, Revesz T. 2011. Globular glial tauopathies (GGT) presenting with motor neuron disease or frontotemporal dementia: An emerging group of 4-repeat tauopathies. *Acta Neuropathol,* 122(4):415-28. (*joint first author)

Djamshidian A, O'Sullivan SS, Sanotsky Y, Sharman S, Matviyenko Y, Foltynie T, Michalczuk R, Aviles-Olmos I, Fedoryshyn L, Doherty KM, Filts Y, Selikhova M, Bowden-Jones H, Joyce E, Lees AJ, Averbeck BB. 2012. Decision making, impulsivity, and addictions: do Parkinson's disease patients jump to conclusions? *Mov Disord*, 27(9):1137-45.

Doherty KM, Rohrer JD, Lees AJ, Holton JL, Warren J. 2013. Primary progressive aphasia with parkinsonism: Clinicopathological case. *Mov Disord*, 28(6):741-6.

Doherty KM, Silveira-Moriyama L, Parkkinen L, Healy DG, Farrell M, Mencacci NE, Ahmed Z, Brett FM, Hardy J, Quinn N, Counihan TJ, Lynch T, Fox ZV, Revesz T, Lees AJ, Holton JL. 2013. Parkin Disease – A clinicopathological entity? *JAMA Neurol*, 70(5):571-9.

Doherty KM, Hardy J. Parkin disease and the Lewy body conundrum. 2013, *Mov Disord*, 28(6):702-4.

*List of abbreviations*

6-OHDA 6-Hydroxydopamine

ANOVA Analysis of Variance

AP Anterior-posterior

CI Confidence interval

COX cyclo-oxygenase

CK creatine kinase

COMTi Catechol-O-methyl transferase inhibitor

CT Computerised tomography

DA Dopamine agonist

DaTSCAN Dopamine transporter scan

DBS Deep brain stimulation

DLB Dementia with Lewy bodies

DNA Deoxyribonucleic acid

EMG Electromyography

FAB Frontal assessment battery

FES Functional electrical stimulation

FSHD Facioscapulohumeral muscular dystrophy

H&Y Hoehn and Yahr

IoN Institute of Neurology

L-dopa L-3,4-dihydroxyphenylalanine

LEDD L-dopa equivalent daily dose

LED L-dopa equivalent dose

LSVT Lee Silverman voice treatment

MAO-Bi Monoamine oxidase B inhibitor

MDS Movement Disorder Society

MoCA Montreal cognitive assessment

MPTP 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

MRI Magnetic resonance imaging

MSA Multiple system atrophy

MUPs Motor unit (action) potentials

MWU Mann-Whitney U test

NHNN National Hospital for Neurology and Neurosurgery

PD Parkinson's disease

PIGD Postural instability/gait difficulty

PSP Progressive supranuclear palsy

QSBB Queen Square Brain Bank

RA rectus abdominis

RF Royal Free

SD Standard deviation

SDH Succinate Dehydrogenase

TPAD thoraco-pelvic anterior distraction

UCL University College London

UCLH University College London Hospitals

UK United Kingdom

UPDRS Unified Parkinson's Disease Rating Scale

VAS Visual analogue scale

# *Table of Contents*

*List of Tables*

*List of Figures*

# Chapter 1: Postural deformities in Parkinson's disease – a review of the literature

*Introduction*

## Overview of thesis

Clinical examination in patients with Parkinson's disease (PD) tends to focus on finding the cardinal disease features that are required to make a firm diagnosis or assess response to treatment, namely bradykinesia, resting tremor, rigidity and later in the disease, impairment of postural reflexes (Hughes et al, 1992). Although not part of the diagnostic criteria, abnormal posture is a commonly recognized part of the Parkinsonian portrait. This introductory chapter reviews the literature, establishing the current knowledge and thinking regarding axial deformities of the trunk in Parkinson's disease. Obstacles for future research and neglected areas of study are identified and addressed in the studies which follow.

## Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disease in older people (following Alzheimer's disease) and is estimated to have a prevalence of 0.3% or 1% in those aged over 60 years (Nussbaum and Ellis, 2003). The cause remains largely unknown with just a few convincing acquired causes described in the past century – post-encephalitic Parkinson's following encephalitis lethargica related to the Spanish flu and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in drug users in the 1970's and 80's (Langston et al, 1983), but it is estimated that between 10-40% of PD may be explained by Mendelian genes and PD high risk loci (Hardy, 2010).

Clinical presentation of PD often incorporates the motor features of the disease – namely tremor, limb stiffness or slowed movements. It is often asymmetric at onset and progresses to involve the contralateral limb. The disease is classically staged using the Hoehn and Yahr (H&Y) scale (Hoehn and Yahr, 1967) which gives immediate information about whether the disease affects one or both sides of the body and whether balance is impaired. Disease severity is assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) recently updated by the Movement Disorder Society (MDS) (Goetz et al, 2008). Non-motor features of the disease are increasingly recognized and include REM sleep behaviour disorder, depression, apathy and constipation. The cardinal features of PD that are used for clinical diagnosis stem from retrospective review of the clinical features in pathologically confirmed cases (Hughes et al, 1992). The neuropathological hallmark of sporadic PD is severe depletion of pigmented neurons in the ventral tier of the substantia nigra pars compacta and the finding of Lewy bodies in those cells that remain. The loss of these dopamine containing neurons are felt to give rise to the clinical signs of bradykinesia and rigidity. Dopamine is a neurotransmitter necessary for smooth continuous movement and these clinical features reflect its depletion in the nigrostriatal pathways. Lewy body pathology in other subcortical and cortical regions is thought to give rise to the other disease features (e.g. olfactory bulb – hyposmia, cortices – Parkinson's disease dementia (PDD) or Lewy Body Dementia (LBD)).

## Postural deformities in Parkinson's disease

Patients with PD or atypical parkinsonism often present with abnormal posture. A retrospective observational study found that a third of PD patients had a deformity of their limbs, neck or trunk (Ashour and Jankovic, 2006). The most recognised type is the classical stooped simian appearance, with flexion of the hips, knees and rounding of the shoulders (Figure 1), but an important subset of patients show more severe abnormalities of posture or spinal alignment, leading to significant disability. These severe postural deformities include camptocormia, antecollis, Pisa syndrome and scoliosis. The underlying pathophysiology of these deformities is largely unknown, and their management remains difficult.

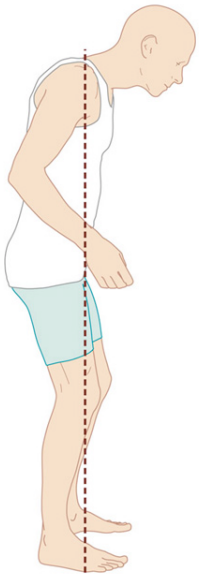


**Figure 1: Stooped posture in Parkinson's disease**

The classical 'stooped' appearance of a patient with Parkinson's disease with mild hip and knee flexion and rounding of the shoulders.

This chapter reviews the prevalence, clinical presentation, and current treatment options of the axial postural deformities encountered in parkinsonism. The possible pathophysiological mechanisms are reviewed and areas which require further study are emphasised. Although many patients present with a combination of deformities in both the sagittal and coronal plane they are separated according to the predominant plane of deformity.

## Methodology, search strategy and selection criteria

Analysis was limited to articles related to deformities of the axial skeleton. Much of the literature in this area consists of descriptive studies, such as prevalence reports, case series or observational studies, some of which are case-control. Relevant studies of all types were reviewed if they added new knowledge in this area. This was not a systematic review. All papers with any reference to the listed deformities were read in order to inform other aspects of the studies undertaken in this thesis.

Potential papers were identified by searching PubMed from 1966 until February 2013 using the terms “postural abnormalities”, “camptocormia”, “bent spine syndrome”, “Pisa syndrome”, “scoliosis”, “lateral flexion”, “dropped head syndrome”, “antecollis”, “retrocollis” and “Parkinson’s”. Selected articles were also obtained from the reference lists of papers identified by the PubMed search, from searches of the authors’ own files and of the National Hospital for Neurology and Neurosurgery library for historical papers.

*Sagittal plane deformities*

## Camptocormia

Definition

The term ‘camptocormia’ is used to describe a distinctive and much more pronounced manifestation of the stooped posture first described by James Parkinson (Parkinson, 1817) with flexion originating in the thoracic or lumbar spine (Figure 2a).

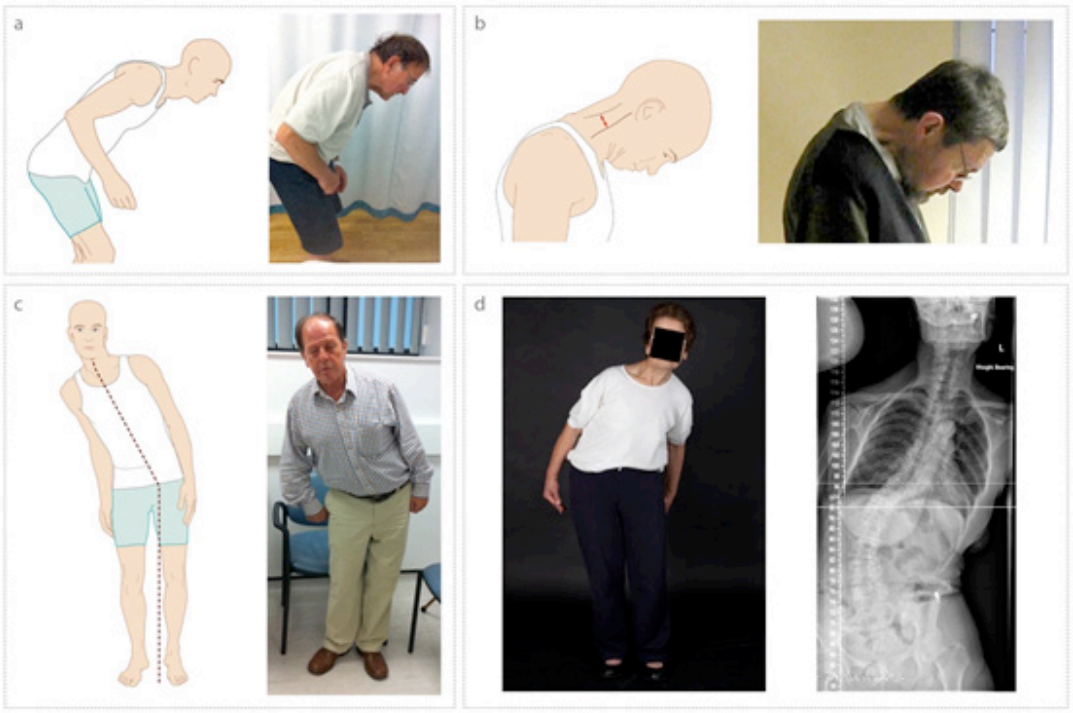



**Figure 2: Sagittal and coronal plane deformities in Parkinson’s disease**

Sagittal plane deformities (a: camptocormia, b: antecollis) and coronal plane deformities (c: Pisa syndrome, d: scoliosis).

Camptocormia is also referred to as 'bent spine syndrome', a term used in the past to describe soldiers who developed a persistently bent spine as a manifestation of what we now call post-traumatic stress disorder (Hurst, 1918). There are no consensus criteria for diagnosing camptocormia but most authors use an arbitrary figure of at least $45^0$ thoracolumbar flexion apparent when standing or walking, which resolves when the patient lies supine (Azher and Jankovic, 2005, Tiple et al, 2009, Ashour and Jankovic, 2006). Some have divided the camptocormia into upper or lower depending on the location of the inflection point in the spine (Furusawa et al, 2012b). Most often the diagnosis is made by subjectively assessing the patient's posture.

## Epidemiology

The term camptocormia was first used to describe bent spine in a PD patient in 1999 (Djaldetti et al, 1999). Subsequent studies describe prevalence rates between 3 and 17.6% in PD (Table 1) (Ashour and Jankovic, 2006, Tiple et al, 2009, Abe et al, 2010, Lepoutre et al, 2006, Seki et al, 2011). This wide range likely reflects the different thresholds that physicians use for diagnosing the phenomenon, the lack of a clear clinical definition and the different populations studied. The prevalence of camptocormia may vary between countries - reflecting a genetic difference in skeletal shape between different ethnic groups (Zarate-Kalfopulos et al, 2012), although two recent Japanese studies provided extremely varied prevalence rates (Seki et al, 2011, Abe et al, 2010). Most reports show a positive association between camptocormia and disease severity, with camptocormia sufferers tending to have more advanced parkinsonism than those without (Ashour and Jankovic, 2006, Margraf et al, 2010, Tiple et al, 2009, Bloch et al, 2006, Seki et al, 2011, Kashihara and Imamura, 2012). Patients with camptocormia also tend to be older (Djaldetti et al, 1999, Seki et al, 2011). On average, camptocormia presents 6-8 years following onset of parkinsonism (Azher and Jankovic, 2005, Margraf et al, 2010, Spuler et al, 2010, Bloch et al, 2006, Lepoutre et al, 2006, Djaldetti et al, 1999, Seki et al, 2011). Some report a higher prevalence in females and attribute this to osteoporosis (Kashihara and Imamura, 2012) while other studies favour a higher prevalence in males (Lepoutre et al, 2006).

| | Country | PD patients | Prevalence (%) | Diagnostic criteria |
|---|---|---|---|---|
| **Camptocormia** | | | | |
| Seki, 2011 | Japan | 531 | 4 | $45^0$ TLF |
| Abe, 2010 | Japan | 153 | 18 | $45^0$ TLF |
| Tiple, 2009 | Italy | 275 | 7 | $45^0$ TLF |
| Lepoutre, 2006 | France | 700 | 3 | TLF |
| Ashour, 2006 | USA | 164 | 12 | $45^0$ TLF |
| **Antecollis** | | | | |
| Ashour, 2006 | USA | 164 | 6 | $>45^0$ Neck flexion |
| Kashihara, 2006 | Japan | 252 | 6 | Neck flexion |
| Fujimoto, 2003 | Japan | 131 | 5 | NA |
| Yamada, 2003 | Japan | 126 | 6 | NA |
| **Pisa syndrome / scoliosis** | | | | |
| Bonnani, 2007 | Italy | 1400 | 2 | LF |
| Baik, 2006 | Korea | 97 | 33 | Radiograph (Cobb method) |
| Ashour, 2006 | USA | 164 | 9 | Lateral curvature |
| Grimes, 1987 | UK | 103 | 60 | Clinical, radiograph in 50% |
| Indo, 1980 | Japan | 70 | 31 | Clinical |
| Serratrice, 1976 | France | 140 | 13 | Clinical, then radiograph |
| Duvoisin, 1975 | UK | 21 | 91 | Clinical |
| Onuaguluchi, 1964 | UK | 33 | 15 | NA |
| Sicard, 1905 | France | 17 | 47 | NA |

**Table 1: Prevalence studies of postural deformities in PD**

The prevalence of camptocormia, antecollis and Pisa syndrome/scoliosis from review of the literature.

Key: TLF thoracolumbar flexion; NA data not available; LF lateral flexion

## Clinical presentation

Patients may not complain about their abnormal posture until it interferes with their mobility or vision, especially if onset of the deformity was gradual. In some patients the onset is subacute, with development of significant flexion over days to months (Margraf et al, 2010, Lepoutre et al, 2006, Spuler et al, 2010). Back pain is common and it is often associated with a prior history of back problems, degenerative spinal disease or surgery (Azher and Jankovic, 2005, Djaldetti et al, 1999, Margraf et al, 2010, Tiple et al, 2009, Bloch et al, 2006, Seki et al, 2011), but it is not clear if this observed association is a risk factor in the development of camptocormia. Some patients report a feeling of being pulled forward or a sensation of tightening or contraction in their abdomen (Azher and Jankovic, 2005, Kataoka et al, 2012), but abdominal jerking or contractions are rarely reported or observed in PD patients with camptocormia (Thani et al, 2011). Posture is often reported to deteriorate further upon walking, or if patients undertake strenuous physical activity (Margraf et al, 2010). If the deformity is long established with secondary fixed changes, patients may complain of breathlessness due to restricted lung capacity, difficulty swallowing or of difficulty lying flat in bed due to hip or knee contractures; the latter can be accompanied by skin irritation in the flexed segment (Bloch et al, 2006).

Examination may reveal a reversible deformity that patients can overcome when asked to stand up straight or stand against a wall, but in others the abnormal posture is more fixed, and does not improve until the patient lies flat. Some believe that the manoeuvre of standing against a wall to enable erect posture represents a *geste antagoniste* or sensory trick, but it may be that this is simply a safe surface in which patients can attempt to stand as straight as possible without the risk of falling backwards. Neurological examination often reveals marked axial rigidity (Bloch et al, 2006, Lepoutre et al, 2006). Strength of trunk and hip extension is normal unless testing is precluded by fixed posture or pain (Lepoutre et al, 2006). The paraspinal muscles may have a wooden consistency and the rectus abdominis often feels tense (Azher and Jankovic, 2005). There may be compensatory hyperextension of the neck to maintain

horizontal gaze. There is often mixed deformity with deviation in the coronal plane also.

## Differential diagnosis

Diagnosing camptocormia in the setting of parkinsonism is based on clinical examination alone, as aetiological investigation of the deformity is hindered by the limited knowledge in this area. Nevertheless, some specific findings might suggest alternative diagnoses. For example, weakness of truncal extension suggests concomitant myopathy or anterior horn cell disease, and should trigger further focused investigations. Fixed deformity that persists even when supine implies osteoarticular changes, which can either be causative (e.g. vertebral fractures, ankylosing spondylitis) or be secondary to the deformity (e.g. acquired degenerative spondyloarthropathy). A list of differential diagnoses and tailored ancillary investigations is given in Figure 3.

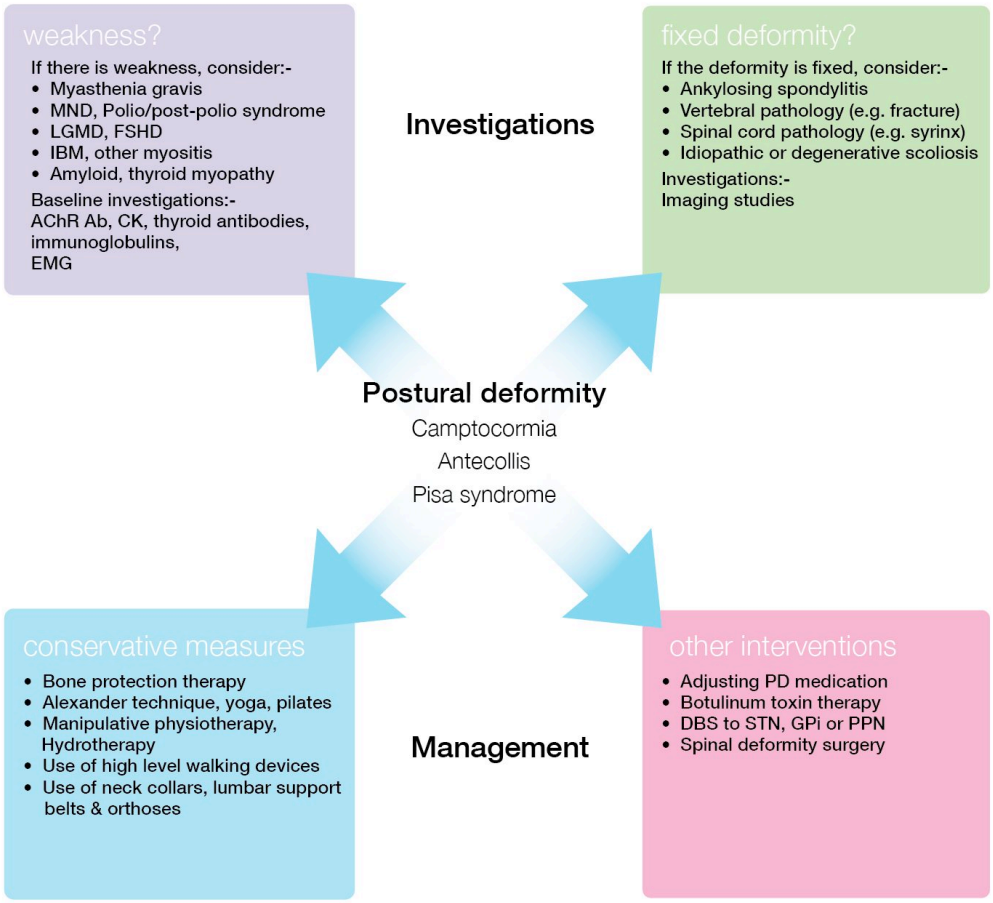



**Figure 3: Considerations and management options in Parkinson's related deformity**

Differential diagnoses, investigations and management options for postural deformity encountered in Parkinson's disease based on review of the current literature.

Key: MND motor neuron disease; LGMD limb girdle muscular dystrophy; FSHD facioscapulohumeral dystrophy; IBM inclusion body myositis; Ab antibody; CK creatine kinase; EMG electromyography; DBS deep brain stimulation; STN subthalamic nucleus; GPi globus pallidus interna; PPN pedunculopontine nucleus.

## Treatment

### *Drugs*

It is generally accepted that camptocormia is not a levodopa-responsive phenomenon (Djaldetti et al, 1999, Azher and Jankovic, 2005), although one author reported a modest improvement in forward flexion when patients were 'on' drug as opposed to 'off' (Bloch et al, 2006). It also appears that PD patients with camptocormia are sometimes less levodopa responsive than those without this deformity and have fewer levodopa-induced limb dyskinesias (Bloch et al, 2006). This may be because camptocormia is associated with a more severe parkinsonian phenotype ('postural deformity variant' parkinsonism) or it may simply reflect long standing disease with less effective 'on' time. Some reports have also suggested that commencement of dopamine agonists has correlated temporally with the onset of camptocormia with their cessation resulting in an improvement to the posture (Kashihara and Imamura, 2012), an association which is loosely remarked upon in many postural deformities in PD. Anticholinergics are often prescribed for their anti-dystonic properties in patients under the age of 65 years, but there is no evidence to support their use. Botulinum toxin injection to the rectus abdominis, iliopsoas or selected paraspinal muscles groups has been employed, mainly in patients deemed to have a predominantly dystonic element to their deformity. Azher and Jankovic have found this successful in selected patients (Azher and Jankovic, 2005) but few have reproduced their positive results (Von Coelln et al, 2008, Gerton et al, 2010, Fietzek et al, 2009, Colosimo and Salvatori, 2009). Recently a Japanese group have reported success in 75% of their patients after repeat injections of lidocaine into the external oblique muscles for 'upper camptocormia' when combined with a rehabilitation programme focusing on truncal extension. The mechanism is speculated to be that of blocking dystonic excitation (Furusawa et al, 2012a).

*Conservative*

Focused manipulative physiotherapy, hydrotherapy and the use of abdominal binders, corsets or spinal braces (orthotics), are often tried in camptocormia, but are rarely successful for a sustained period and have little to no evidence base. Care must be taken not to cosmetically overcorrect the stooped posture, as a sudden or uncompensated change to sagittal balance may worsen the risk of falling backwards (Bloem et al, 1999). De Seze reports the use of a spinal orthotic device which aims to induce a lumbar lordosis in patients with camptocormia (de Seze et al, 2008). The outcomes in the five tested PD patients were good in terms of improvements in quality of life, pain and sagittal balance. Follow-up radiographs showed improved lumbar lordoses. Patients wore the orthotic device on average for seven hours per day, suggesting good outcomes may require a motivated and compliant patient. There is a single report of a patient where the camptocormia was completely relieved when he wore a low slung backpack (Gerton et al, 2010). This may be a more attractive option for patients who do not want to wear a spinal brace but further study is warranted. High frame walking aids with forearm support are effective strategies to improve patients' mobility, posture and visual perspective and have been used to good effect in camptocormic patients (Schroeteler et al, 2011). General therapeutic options for the various postural deformities are suggested in Figure 3.

*Advanced*

Deep brain stimulation (DBS) of the subthalamic nuclei (STN) has been used as a potential treatment for camptocormia in PD, but outcomes have varied from excellent improvements (Yamada et al, 2006, Hellmann et al, 2006, Sako et al, 2009, Asahi et al, 2011, Lyons et al, 2012), to only mild improvement or no benefit (Capelle et al, 2010, Upadhyaya et al, 2010, Allert et al, 2011). A single non-responder from a series of four was found to have marked paraspinal muscle atrophy on CT imaging which the authors speculate may have precluded the effect of STN-DBS on axial posture. They went on to summarise the DBS literature to quote a figure of 66.7% (16/24) cases improved following STN stimulation and suggest that careful patient selection may impact outcome (Asahi et al, 2011). The pallidum is another potential target to treat

camptocormia due to idiopathic axial dystonia (Capelle et al, 2010, Hagenacker et al, 2013) but the literature in PD patients with camptocormia is limited to only six cases, with no improvement to the posture reported in two, modest improvement in three (Upadhyaya et al, 2010, Micheli et al, 2005, Capelle et al, 2010, O'Riordan S, 2009) and good improvement in one who had a dystonic phenotype with involuntary abdominal contractions on walking (Thani et al, 2011). There has been some interest in the pedunculopontine nucleus (PPN) as a potential stimulating target in patients with PD, but the evidence is more specific for freezing of gait and postural instability rather than postural deformity (Bloch et al, 2006, Strafella et al, 2008, Pahapill and Lozano, 2000).

A Japanese group reported postural improvements following spinal cord stimulation in patients with intractable lower back or leg pain. They didn't describe the particular postural abnormality in their 15 PD patients but reported an improvement in UPDRS item 28 (posture) from a mean 2.4 to 1.8 three months post-operatively (but this subsequently increased to a score of 2.1 twelve months post-operatively) (Agari and Date, 2012).

Spinal surgery has been used to correct postural deformity in patients with PD, in particular when medical measures have failed. This approach has significant complications and often requires revision surgery, although posture improves in some (Upadhyaya et al, 2010, Koller et al, 2010, Peek et al, 2009, Wadia et al, 2011, Babat et al, 2004, Bourghli et al, 2012). When surgery is undertaken long segment fixation is recommended (Sutter et al, 2012, Bourghli et al, 2012, Siewe et al, 2013).

## Antecollis

### Definition

Antecollis or dropped head syndrome in parkinsonian disorders refers to a forward flexion of the head and neck. When mild, this may be seen as part of the stooped posture in PD, but some patients present with what is called a disproportionate antecollis: neck drop which is more pronounced than expected relative to the flexed posture of the trunk and limbs (Quinn, 1989, van de Warrenburg et al, 2007b). The term 'dropped head syndrome' is sometimes used to describe the marked neck flexion, but is more often reserved for neuromuscular disorders such as myasthenia gravis, polymyositis and motor neuron disease (Lange et al, 1986) where it is associated with weakness of neck extension (literally causing the head to drop forward).

### Epidemiology

Antecollis has been recognized only fairly recently as a feature of parkinsonism (Jorens et al, 1989). It is a relatively common feature of multiple system atrophy (MSA) where the antecollis is somewhat fixed, unlike idiopathic spasmodic torticollis (Quinn, 1989). Ashour & Jankovics' retrospective study quotes a high prevalence of 42.1% for this deformity in patients with MSA (Ashour and Jankovic, 2006), whereas the average figure is much lower at 5.8% in PD (Yamada et al, 2003, Ashour and Jankovic, 2006, Kashihara et al, 2006, Fujimoto, 2006). In a series of 15 PD patients, antecollis was more often found in women and in patients whose prominent parkinsonian signs were rigidity and akinesia (Kashihara et al, 2006). As with other postural deformities, ethnicity of the study population influences the prevalence, with more case reports of antecollis originating in Japan than elsewhere (Uzawa et al, 2009).

### Clinical presentation

Antecollis can occur with a subacute onset over weeks or months (Lava and Factor, 2001). It may present prior to the other motor features of PD (Kashihara et al,

2006, Savica et al, 2012) but usually occurs several years into the disease. Patients may complain of pain in the posterior aspect of the neck, or develop problems secondary to neck flexion (difficulty swallowing, excessive drooling, or visual limitation). In early stages hypertrophy and active spasms may be visible in various anterior and posterior neck muscles, but after some time overstretching of posterior neck muscles and a 'woody' feel on palpation, particularly of the splenius capitis and trapezius become prominent features (van de Warrenburg et al, 2007b). Most studies report normal strength on testing residual neck extension (Yoshiyama et al, 1999, Kashihara et al, 2006, van de Warrenburg et al, 2007b), and some note prominent contractions in sternocleidomastoid muscles, limiting voluntary neck extension (Yoshiyama et al, 1999, Fujimoto, 2006). It is likely that the prevertebral deep neck flexors are also involved in antecollis development but these are not easily evaluated without invasive testing. Unlike idiopathic cervical dystonia, there is no *geste antagoniste* in PD or MSA that can improve the abnormal neck posture (Boesch et al, 2002). Antecollis in PD is often associated with markedly increased axial tone, although patients might still be capable of passive extension to the normal position. In other patients, the antecollis may become a fixed deformity, even shortly after onset (Figure 2b) (Spuler et al, 2010).

## Differential diagnosis

Investigation of antecollis should be guided by examination findings (Figure 3). Antecollis is often associated with a limited range of movement as the deformity becomes more longstanding, but if there is striking limitation of neck movement appearing subacutely or when pain is excessive, imaging is necessary to rule out pathology in the cervical spinal cord. Other locations in which central lesions can result in secondary antecollis include the basal ganglia, brainstem and cerebellum (LeDoux and Brady, 2003, Funabe et al, 2013). The most common alternative diagnosis to the finding of antecollis in PD is MSA, where antecollis is frequent. Recent reports have also drawn attention to a possible role for medication-induced changes in neck postures. Antecollis may be an 'off' phenomenon, or it may develop as dyskinesias appear in relation to increases in dopaminergic medications, and so fluctuations of antecollis and its relationship to medication times should be enquired about. On the other hand, several

case reports have suggested that antecollis may be induced by dopamine agonist therapy (seven patients received pramipexole, five cabergoline, two pergolide, and in two the drug was not specified)(Uzawa et al, 2009, Suzuki et al, 2008, Fujimoto, 2006, Taguchi et al, 2008) or amantadine (Kataoka and Ueno, 2011). These medications should therefore be stopped on a trial basis if there is a close temporal association to the onset of the syndrome, although the antecollis is not necessarily reversible, particularly when medication is stopped late (Suzuki et al, 2008, Taguchi et al, 2008).

Weakness of residual neck extension should prompt a further neuromuscular work-up as myopathy has been associated with this phenomenon in PD patients (Savica et al, 2012). Myasthenia gravis must be considered if the patient reports double vision, effortful speech or symptoms suggestive of fatigue. There have been occasional reports describing co-incidental PD and myasthenia gravis in patients presenting with antecollis (Fasano et al, 2008, Unal-Cevik and Temucin, 2009). Weakness of neck extension can also be a presenting feature of motor neuron disease. In PD patients with antecollis without weakness, electromyography and muscle biopsy findings may be abnormal (and some investigators consider patients to have both dystonia and myopathy underlying their abnormal head positioning (Savica et al, 2012)), but such findings are often non-specific and non-diagnostic in terms of cause or effect of the antecollis (van de Warrenburg et al, 2007b).

### Treatment

Some PD and MSA patients reported improved head position following treatment with levodopa, but this was not a consistent finding (Yoshiyama et al, 1999, van de Warrenburg et al, 2007b, Kashihara et al, 2006, Jorens et al, 1989, Boesch et al, 2002, Savica et al, 2012). Muscle relaxants such as clonazepam may be helpful (Kashihara et al, 2006). Botulinum toxin therapy is usually attempted if there are active dystonic spasms on examination, but benefit was reported in only three of 13 patients treated with injection of levator scapulae or sternocleidomastoid muscles (van de Warrenburg et al, 2007b). Botulinum toxin treatment of prevertebral deep neck flexors (longus colli and longus capitis) has been reported as beneficial but required CT guidance in one case

(Herting et al, 2004) and EMG in others (Glass et al, 2009, Flowers et al, 2011). Other neck muscles such as the scalene and submental groups may contribute to antecollis and the approach to each patient should be tailored according to the examination findings (Flowers et al, 2011). One group report a dramatic response to steroids in 3 PD patients whose dropped head was attributed to neck extensor myopathy (Hemmi et al, 2011). Intensive physiotherapy and the use of neck collars may be of benefit although supporting evidence in the literature is lacking (Lin et al, 2013). Few reports exist of management with surgical fusion (Pereira et al, 2010) and DBS (Yamada et al, 2003, Oliveira et al, 2012), likely last resorts to be reserved until more conservative measures have been tried.

## Retrocollis

Retrocollis is an abnormal neck posture, with the head held in extension. It is associated with severe axial rigidity, and is most typically encountered in patients with Progressive supranuclear palsy (PSP) and in patients exposed to neuroleptics. It also occurs as a subtype of primary cervical dystonia (Papapetropoulos et al, 2008). Retrocollis is hardly ever seen in PD, and should therefore be regarded as a prominent ‘red flag’, in particular signalling a diagnosis of PSP.

*Coronal plane deformities*

## Pisa syndrome & scoliosis

Pisa syndrome and scoliosis are discussed jointly here, as they share not only the plane of deformity but also the body segment involved.

### Definitions

Pisa syndrome refers to a marked lateral flexion or listing of the trunk, which is typically mobile (resolving, for example, upon lying down). This postural deformity was first described as a truncal dystonia or 'pleurothotonus', occurring as a side effect of antipsychotic treatment (Ekbom et al, 1972). More recently, Pisa syndrome has been described in PD (Villarejo et al, 2003). It has also been described in association with Alzheimer's disease treated with cholinesterase inhibitors (Vanacore et al, 2005) and as an idiopathic phenomenon (Bhattacharya et al, 2000) (Figure 2c).

Scoliosis is defined as a lateral curve of the spine combined with rotation of the vertebrae and in the orthopaedic literature has specific radiological features (Schwab et al, 2002, Vrtovec et al, 2009b, Vrtovec et al, 2009a). For this reason, it should not be used as a descriptive term in PD patients with lateral trunk flexion, unless there is radiological confirmation. Many early 'scoliosis' studies did not utilize radiology for the diagnosis, and likely referred to some 'Pisa syndrome' cases.

There are no diagnostic criteria for Pisa syndrome, although Bonanni and colleagues proposed a detailed definition for lateral axial dystonia as: $>15^0$ lateral flexion of the trunk, increasing during walking, not present when supine, and in the absence of any mechanical restriction to trunk movement (i.e. degenerative spinal disease), with continuous electromyography (EMG) activity in the lumbar paraspinal muscles ipsilateral to the bending side (Bonanni et al, 2007). Bonanni's definition is limiting as the mechanism may not be dystonic, and EMG studies should not be required to define

a clinical syndrome.

## Epidemiology

A tilting to one side is common in the later stages of PD. Scoliosis is reportedly more common in PD than the normal elderly population, with prevalence figures ranging from 8.4–90.5% in parkinsonism (Baik et al, 2009, Ashour and Jankovic, 2006, Grimes et al, 1987, Duvoisin and Marsden, 1975, Indo and Ando, 1980, Serratrice and Schiano, 1976, Sicard and Alquier, 1905) and 8.5–60% in PD (Table 1) (Baik et al, 2009, Grimes et al, 1987, Indo and Ando, 1980, Serratrice and Schiano, 1976, Ashour and Jankovic, 2006). However, these prevalence rates reflect clinical observation without radiological confirmation, and therefore may not accurately represent 'true scoliosis'. The high variation in prevalence likely reflects the different types of parkinsonism studied (some older papers included patients with post-encephalitic parkinsonism, in which all postural deformities were very commonly observed) (Martin, 1965a), the variable disease duration, and the different treatments received. Similar caveats also explain the conflicting evidence about the relationship of scoliosis with disease duration and severity, treatments options and presence of dyskinesias (Grimes et al, 1987, Ashour and Jankovic, 2006). Some suggest that lateral flexion deformity is more likely in patients with markedly asymmetrical disease (Tassorelli et al, 2012).

## Clinical presentation

In early stages most patients are not aware of any lateral flexion (Duvoisin and Marsden, 1975). Pisa syndrome can develop in a chronic fashion (insidious at first, with gradual worsening) or with a subacute onset followed by rapid deterioration over months (Yokochi, 2006). It may first be noticed as the tendency of a patient to tilt to one side when sitting in a chair, with subsequent lateral flexion when they walk. When the deformity advances patients may develop pain (Martin, 1965a, Di Matteo et al, 2011), dyspnoea, or unsteadiness leading to falls. On examination the patient will sit, stand or walk with an involuntary lean that is consistently to one side. Patients may have impaired perception of the vertical position, and when asked to stand up straight believe

they are already doing so, hence actively moving the patient to the midline may cause them to feel unbalanced (Proctor et al, 1964).

There has been debate whether patients with lateral trunk flexion (Pisa syndrome or scoliosis) lean towards or away from their predominant parkinsonian symptom side. Most investigators found that patients tended to lean away from the most affected side (Martin, 1965a, Onuaguluchi, 1964, Duvoisin and Marsden, 1975, Serratrice and Schiano, 1976, Di Matteo et al, 2011, Tassorelli et al, 2012, Vitale et al, 2011), and only few authors found no association between the direction of the curve and the laterality of PD (Grimes et al, 1987, Baik et al, 2009).

### Differential diagnosis

Pisa syndrome is simply a clinical description of the finding of lateral flexion of the trunk. If there is any evidence of weakness on individual muscle testing co-existent neurological conditions ought to be sought. Spinal imaging with calculation of the Cobb angle is required for diagnosing and quantifying scoliosis (Cobb, 1948).

As with antecollis, there are reports that Pisa syndrome may be an adverse effect of medication. The archetype is that of Pisa syndrome secondary to dopamine-blocking agents (Ekbom et al, 1972), but more recent work also points to development of Pisa syndrome with a close temporal relationship after changes in dopaminergic medication (either start of a new drug, or a dose increase of existing medication)(Cannas et al, 2009). Specifically, Pisa syndrome occurred upon instigation (one patient), increase (six patients) or decrease (one patient) of dopaminergic medication, and at an interval of 15 days to three months from medication change. Conversely, Pisa syndrome disappeared following reversal of the medication change after 10 days to three months (Cannas et al, 2009), although like antecollis it can be irreversible. It has also been reported to develop subacutely in association with rasagiline (Fasano et al, 2011). It is therefore important to review recent alterations to the patient's medication and to note any non-PD therapies that might be contributing (neuroleptics, lithium carbonate, valproic acid, antidepressants, anti-emetics, cholinesterase inhibitors) (Vanacore et al, 2005, Salazar et

al, 2008, Ekbom et al, 1972, Suzuki and Matsuzaka, 2002).

There are two reports of Pisa syndrome developing in patients following pallidotomy, at a time interval of 4-9 years post-surgery (van de Warrenburg et al, 2007a, Spanaki et al, 2010).

## Treatment

Pisa syndrome in its early mobile phase may be indicative of prominent axial dyskinesia and hence may resolve when dopaminergic therapy is modified (Cannas et al, 2009), but this is less successful in patients with longstanding postural deformities (Yokochi, 2006, Di Matteo et al, 2011). Drug treatment approaches include anticholinergics and clozapine (Bonanni et al, 2007, Bhattacharya et al, 2000). Bonanni and colleagues performed a blinded cross-over trial of botulinum toxin injected into the lumbar paraspinals versus placebo in nine patients with Pisa syndrome; six of their nine patients experienced improvement of their posture and seven opted to continue receiving botulinum toxin treatment at the end of the study (Bonanni et al, 2007). Subthalamic DBS has been applied in ten PD patients with Pisa syndrome, but the findings were inconclusive (Umemura et al, 2009).

Spinal orthotic appliances have been tried in some patients with scoliosis or Pisa syndrome, but they are often not tolerated by patients. Patients with clinical and imaging evidence of underlying myelopathy or radiculopathy should be referred for surgical intervention (Upadhyaya et al, 2010). Results of spinal surgery to treat Pisa syndrome and scoliosis in PD patients have been mixed. There are concerns that patients continue to flex laterally postoperatively (Tabamo et al, 2000), and often require revision surgery (Babat et al, 2004, Koller et al, 2010, Bourghli et al, 2012).

## *Pathophysiology of Parkinsonian postural deformity*

The pathophysiology of axial postural abnormalities in PD is not well understood, but a number of different causes have been proposed. Beginning with the evidence from animal studies for central causes leads to discussion of the proposed central mechanisms (dystonia, rigidity, proprioceptive disintegration), followed by proposals attributed to a peripheral process (myopathy, skeletal & soft tissue changes).

## Central mechanisms

### Animal studies and lesioning

In the case of scoliosis and Pisa syndrome it is likely that an asymmetrical central process plays a role in the tendency to lean to one particular side. Studies in a rat model found that chemical degeneration of an entire nigrostriatal pathway on one side produced marked spontaneous turning ipsilateral to the lesion (Ungerstedt et al, 1969). Similarly, hemiparkinsonism in rats (caused by injecting 6-hydroxydopamine into the left ventral tegmental area) led to development of a marked ipsilateral deviation and scoliosis deformity (Herrera-Marschitz et al, 1990). These experimental observations are consistent with clinical findings that the concavity of the scoliosis and corresponding trunk inclination are usually directed away from the most clinically affected side (Duvoisin and Marsden, 1975). Pisa syndrome can also occur following unilateral pallidotomy. Specifically three patients developed Pisa syndrome to the right following left pallidotomies 4, 8 and 9 years post-surgery (van de Warrenburg et al, 2007a, Spanaki et al, 2010). These findings support a central aetiology for initial development of coronal plane deformities with the resulting muscle changes, tendon shortening and contracture development being followed by degenerative bone and joint changes, leading to possible fixed deformity.

On the other hand the data on central lesions leading to camptocormia or antecollis is sparse and there are no animal models of camptocormia or antecollis. 'Dystonic'

camptocormia has been reported as a complication of stroke in two non-PD patients (Nieves et al, 2001). Both had vascular insults in the right putamen, but the authors do not elaborate on why patients with similar lesions do not develop camptocormia. Bloch et al reported camptocormic PD patients performing poorly on tests of saccadic eye movements pointing to possible neuronal dysfunction in the midbrain (Bloch et al, 2006). Bonneville and colleagues found that camptocormic PD patients had significantly smaller midbrain axial surface areas compared to controls but not compared to PD patients without camptocormia (Bonneville et al, 2008). Some believe the pedunculopontine nucleus is implicated but the correlation appears stronger for gait freezing and postural instability than for postural deformity (Bloch et al, 2006). Basal ganglia lesions have been implicated in development of antecollis (Funabe et al, 2013) as have lesions in the brainstem and cerebellum (LeDoux and Brady, 2003).

## Dystonia

Limb dystonia is a common associated feature in young onset PD. Flexion dystonia has been considered the cause for the characteristic stooped posture of late stage PD although the evidence for this is extremely limited. Support comes from the clinical observation of actively contracting muscles in certain postures (e.g. common in early antecollis, occasionally seen in Pisa syndrome), from anecdotal reports of patients using sensory tricks to overcome their abnormal posture (Azher and Jankovic, 2005, Gerton et al, 2010) and from reports of improvement following botulinum toxin injection (Azher and Jankovic, 2005, Bonanni et al, 2007). Dystonia may be suggested by electromyography, and a few studies have noted continuous paraspinal activity ipsilateral to the bending side (suggestive of dystonia) in Pisa syndrome cases (Bonanni et al, 2007, Fasano et al, 2011) with one detecting hyperactivity in ipsilateral paraspinal muscles in the thoracic, not lumbar region (Tassorelli et al, 2012). However, another study reported the opposite, finding typical dystonic activity in the ipsilateral (to bending side) paravertebral muscles in only three of ten PD patients with Pisa syndrome (Di Matteo et al, 2011). Recently Tinazzi and colleagues described two patterns of muscular activation following EMG study – those with hyperactivity of the lumbar paraspinals ipsilateral to the leaning side and those with hyperactivity of the lumbar

paraspinals contralateral to the leaning side (Tinazzi et al, 2013). They concluded that paraspinal hyperactivity contralateral to the leaning side was probably compensatory for the abnormal lateral flexion. The inability for EMG to differentiate between an active dystonic process and a compensatory response to abnormal trunk leaning should lead us to consider that paraspinal hyperactivity alone should not be used to guide botulinum toxin injection in the case of lateral flexion deformity. There is a risk that one could make a flexed posture worse by disabling the body's natural compensatory attempts.

Most investigators feel that if a dystonic phenomenon is occurring, it likely represents an early and short-lived component of postural deformity development. In those instances in which it develops subacutely in relation to a medication and reverses on cessation of the offending drug, a centrally mediated neurochemical imbalance triggering striatal changes has been proposed as the mechanism (Fasano et al, 2011). This 'dystonic' phenotype is perhaps best seen in younger patients with more mobile postural abnormalities when other dystonic features such as jerking and active muscles spasms may also be evident. Dystonia is more often observed in juvenile and young-onset PD patients and may be associated with genetic parkinsonism such as parkin disease (PARK2) (Inzelberg et al, 2003, Khan et al, 2003, Doherty et al, 2013). In advanced patients, this dystonic element may 'burn out', with secondary soft tissue, muscle and spinal changes taking greater precedence, leading to a more 'fixed' deformity.

### Impaired proprioception and kinaesthesia

Postural control is a complex system involving the integration of sensory information (vestibular, visual and proprioceptive). Regarding the vestibular component, most studies conclude that vestibular dysfunction does not explain postural deficits in PD (Martin, 1965c, Pastor et al, 1993, Pollak et al, 2009, Rascol et al, 1995) although a recent Italian study found evidence of unilateral vestibular hypofunction in 11 PD patients with lateral trunk flexion but of a peripheral type (ocular and labyrinth testing)(Vitale et al, 2011).

Proprioception provides highly accurate information that helps to maintain body

verticality in normal subjects (Vaugoyeau et al, 2008), but studies in PD patients have given inconsistent results. Duvoisin and Marsden described 19 Parkinsonian patients with scoliosis (or Pisa syndrome), only one of which was conscious of a tendency to lean to the side (Duvoisin and Marsden, 1975). They also reported that the scoliosis increased when patients closed their eyes, possibly indicating defective judgement of the visual and postural vertical. Azulay and colleagues supported these findings, showing that PD subjects perform poorly on tasks where the aim is to maintain postural orientation in the vertical plane, with notable deterioration when visual input is removed (Vaugoyeau and Azulay, 2010, Vaugoyeau et al, 2007). They also examined proprioceptive integration using tendon vibration stimulation and showed that a specific involvement of the static proprioceptive does exist causing a specific orientation postural deficit in PD while a dynamic process may be preserved or damaged later in the course of the disease (Vaugoyeau et al, 2011). Many subsequent studies have confirmed that proprioceptive function is abnormal in PD. This evidence was initially restricted to motor control of the limbs, mainly the arms (Sailer et al, 2003, Seiss et al, 2003, Konczak et al, 2007, Keijsers et al, 2005). Recent work has extended these findings, demonstrating that proprioceptive defects also affect axial motor control in the yaw plane (Wright et al, 2010, Carpenter and Bloem, 2010). Whether such proprioceptive defects also affect postural control in the sagittal or coronal plane requires further study, and this would have implications for understanding postural deformities such as camptocormia and Pisa syndrome. To further the proprioceptive theory in camptocormia, there is a study of such patients who underwent muscle biopsy which revealed myopathic changes similar to those found in tenotomised muscles (Wrede et al, 2012). Following tendon excision, muscle tension reflex mechanisms are impaired and the muscle alters with development of core-like lesions in the type 1 fibres associated increased acid phosphatase activity. PD camptocormia paraspinal muscle biopsies are described as similar and this finding adds some weight to a possible proprioceptive mechanism.

Some consider that the development of postural deformity may be a complex compensatory mechanism to reduce risk of falling. The tendency to stoop in PD is protective against falls whereas at the other end of the spectrum patients with PSP due to their overly erect or possibly retrocollic postures have a tendency to fall backwards. On the other hand lateral flexion deformity has been associated with more frequent falling, likely because the centre of gravity is asymmetrically placed (Hayashi et al, 2010).

## Rigidity

Rigidity is defined as a persistent increase in muscle tone which is not velocity dependent. Froment studied changes in Parkinsonian rigidity with posture and concluded that the body had two mechanisms to protect against postural abnormalities: a maintenance stabilisation of muscular contraction (to hold the trunk erect in an unstressed state); and a reactive stabilisation of muscle activation that occurs when posture is disturbed. He suggested that the first mechanism was impaired in PD, and that the second mechanism was in constant use to maintain posture, leading to continual abnormal muscle recruitment and activation - axial rigidity (Broussolle et al, 2007). More contemporary experimental work confirms that patients with PD have a higher axial tone than controls (Wright et al, 2007). In addition, PD patients respond abnormally to perturbations during stance, showing reduced intersegmental flexibility (Horak et al, 2005, Carpenter et al, 2004). PD patients also present a reduced range of spinal movement, especially around the spinal axis (Schenkman et al, 2001, Nikfekr et al, 2002, Carpenter et al, 2004). These deficits may be compensated for with flexion in the sagittal or coronal plane, in order to maintain the centre of gravity within the limits of stability and to prevent falls. Burleigh and colleagues studied the effect of Levodopa on muscle tone in PD patients during quiet stance. They found that lower extremity and trunk muscles were of high amplitude activity (using EMG) in all PD subjects when 'off', but when 'on' muscle activity was reduced, concluding that dopamine depletion results in increased muscle tone during stance which may contribute to postural change (Burleigh et al, 1995). However a condition typified by predominant paraspinal muscle rigidity is stiff person syndrome and it is associated with a hyperlordotic lumbar spine

(Hadavi et al, 2011) the opposite posture of that encountered by patients with camptocormia.

Clinical and animal experiments which demonstrate a tendency to lean away from the more rigid (predominant PD symptom) side in coronal plane deformities also challenges the theory that rigidity is the principal cause of postural abnormalities (Ungerstedt et al, 1969, Di Matteo et al, 2011, Duvoisin and Marsden, 1975, Martin, 1965a, Serratrice and Schiano, 1976, Herrera-Marschitz et al, 1990).

### Drugs

There are a few reports claiming that dopamine agonists can induce or aggravate antecollis (Taguchi et al, 2008, Uzawa et al, 2009, Suzuki et al, 2008) or Pisa syndrome (Cannas et al, 2005, Cannas et al, 2009) in PD, with the onset of the deformity beginning between a few weeks to 18 months after treatment initiation, and usually resolving on stopping the drug. There also exist reports of other medications such as cholinesterase inhibitors, valproate, rasagiline and amantadine leading to deformities but these are simply single case reports or small cases series'(Vanacore et al, 2005, Kataoka and Ueno, 2011, Salazar et al, 2008, Fasano et al, 2011). A proposed mechanism is the imbalance between dopamine, noradrenaline and serotonin levels and how these neurotransmitters regulate axial muscle tone (Villarejo et al, 2003). Most cases have been reported from Japan, and that may reflect a genetic difference in the expression of drug metabolising enzymes and transporters (Cropp et al, 2008). It is important to note that these cases are few, evidence is weak, and the majority of patients taking dopamine agonists do not develop such deformities.

## Peripheral mechanisms

### Myopathy

Evidence for a myopathy has been found on electromyography (fibrillation potentials, small polyphasic MUPs), muscle imaging (fatty infiltration of muscles, muscle atrophy) and muscle biopsy (abnormal histology) in PD patients with abnormal postures (Schabitz et al, 2003, Margraf et al, 2010, Spuler et al, 2010, Gdynia et al, 2009, Lava and Factor, 2001, Wrede et al, 2012). A concomitant specific muscle disease, such as myasthenia gravis or a focal myositis (Wunderlich et al, 2002, Charpentier et al, 2005) proves to be the cause in a few cases, but it has been proposed by some that primary muscle disease could be responsible for antecollis and camptocormia in PD (Margraf et al, 2010, Spuler et al, 2010) though it seems unusual why PD patients would develop such a localised myopathy. Some believe a dysfunctional mitochondrial process may be able to link myopathy with PD, but in other atypical parkinsonian conditions which exhibit frequent postural deformity (such as MSA) there exists no known mitochondrial link (Savica et al, 2012) and a recent study found less evidence of mitochondrial changes in camptocormic versus control paraspinal muscle biopsy (Wrede et al, 2012). Most studies, however, have suggested that myopathic changes when present are non-specific and related to disuse or denervation secondary to the severe primary postural abnormality (Bloch et al, 2006, Abe et al, 2010, Djaldetti et al, 1999, Yoshiyama et al, 1999, Di Matteo et al, 2011, van de Warrenburg et al, 2007b, Lepoutre et al, 2006, Jankovic, 2010).

Some of these discrepancies may be due to the fact that EMG of the axial musculature is technically difficult (particularly for myopathic features that require voluntary activation), normal values for these groups are unclear, superficial testing may miss out relevant deep muscles and the inter-operator reproducibility is poor (Danneels et al, 2001). Imaging changes in paraspinal muscles are often non-specific. Findings on muscle biopsy may reflect age-related change (Gdynia et al, 2009), and information on the histology of paraspinal muscles in PD patients without camptocormia are lacking. Many studies failed to comment specifically on strength in the affected muscle groups

(Margraf et al, 2010, Spuler et al, 2010, Schabitz et al, 2003, Gdynia et al, 2009). A recent study investigated the underlying cause of camptocormia in 63 patients (not restricted to PD) (Laroche and Cintas, 2010). The results showed that 40 patients had a paraspinal myopathy, as evidenced by muscle weakness, typical CT findings (fatty infiltration restricted to the paraspinal muscles) and biopsy findings showing lobular endomysial fibrosis. The remaining 23 patients had another muscle or neurological disorder – such as limb girdle muscular dystrophy, myotonic dystrophy or inclusion body myositis. Within the paraspinal myopathy group there were four patients with PD. Moreover, there were another four patients with PD within the group not meeting the criteria for paraspinal myopathy. This interesting study adds to growing evidence that myopathic changes can occur in PD patients with camptocormia (Laroche and Cintas, 2010), but it seems unlikely that this will prove to be the primary cause in the majority of cases.

A possible consideration is the age at onset of the disorder which may reflect the resulting deformity pattern. Children with myopathy tend to develop exaggerated lordosis in the lumbar spine (e.g. Duchenne muscular dystrophy (Kerr et al, 2008)) but muscle disease of later onset can manifest with camptocormia (Dupeyron et al, 2010, Umapathi et al, 2002, Wood-Allum et al, 2004, Kottlors et al, 2010), which perhaps reflects that it is the time point in development at which the myopathic insult occurred which will affect the pattern of deformity. In a young patient with myopathy stabilisation of the spine is often achieved by locking of the facet joints in a lordotic posture (this is often also accompanied by scoliosis), whereas in the older patient with an established spinal profile, possible anterior degenerative changes and anterior pelvic tilting, the development of lumbar lordosis for spinal stabilisation is precluded and hence they may flex forward.

### Spinal and soft tissue changes

A history of back surgery (e.g. laminectomy), trauma or degenerative spinal conditions is frequent in PD patients with postural deformities, especially in those with camptocormia (Azher and Jankovic, 2005, Margraf et al, 2010, Tiple et al, 2009,

Djaldetti et al, 1999, Abe et al, 2010, Bonneville et al, 2008). These factors are likely to have a direct mechanical effect on posture due to bony and soft tissue changes and it is conceivable that they may trigger a peripherally induced (secondary) dystonic phenomenon in some patients (Bonanni et al, 2007). When pain is present, it may provoke a compensatory posture which is more comfortable and therefore becomes habitual, eventually interacting with the patient's proprioceptive sensory feedback and thus contributing to an abnormal body scheme. Another plausible suggestion is that, in the setting of chronic pain, muscle spasm develops as a protective mechanism to prevent movement about the damaged joint thereby promoting abnormal posture (Di Matteo et al, 2011). In their review on striatal hand and foot deformities in PD, Ashour *et al* considered connective tissue changes as a potential pathophysiological mechanism in the development of deformities, particularly loss of elasticity leading to fibrosis and atrophy and hence fixed contracture development (Ashour et al, 2005). It is possible that similar soft tissue changes also underlie the axial postural deformities and that the striatal hand and foot deformities occur due to the same underlying mechanisms.

## *Conclusion*

This literature review has highlighted many areas in need of clarity. The clinical definition of camptocormia and Pisa syndrome appears to differ between groups and there is no consensus regarding the reversibility or fixity of postural deformities. There is confusion whether camptocormia is a localised disorder of the thoracolumbar spine or a problem of regional (upper/lower) or global spinal curvature, whether it is caused by osteoporosis (especially in women) or whether is simply reflects accelerated aging. Opinion on whether the predominant clinical picture is in keeping with dystonia or myopathy remains divided, the extent of dystonic and myopathic features varying greatly in studies to date. There is a dearth of research on the radiological findings underlying such deformities. Where much work has been done with regards the biomechanics of postural stability and falls in PD, little exists for deformity of posture. Response to dopaminergic therapy is unclear. There are no specific quality of life scales for assessing the effect of postural deformity or grading scales for assessing severity of

abnormal posture in PD patients, which will eventually be required for clinical trials when interventions become available. The relationship between clinical phenotype, neurological findings and underlying orthopaedic findings is often amiss and resultantly many postural syndromes may be being misdiagnosed. Based on these omissions and uncertainties the main aims of this thesis include investigation of the following:-

- Thorough clinical examination of the recognised postural syndromes affecting the trunk in PD and their associated disease features (e.g. reversibility with position, site of deformity)
- Any associations between PD subtype (e.g. tremor predominant, axial akinetic rigid predominant) and severity of posture
- Response of postural deformities to dopaminergic therapy
- Whether PD postural deformity reflects accelerated aging in terms of degenerative spinal disease or whether there exist unique features on radiological examination

# Chapter 2: Clinical spectrum of axial deformities of the trunk in Parkinson's disease

## *Introduction*

Flexion of the trunk and limbs is a characteristic feature of Parkinson's disease which enables the fully established disease to be recognised from a photograph. Despite the prominence of these abnormalities their pathophysiology is still poorly understood and in contrast to bradykinesia they respond poorly to dopaminergic medication and become increasingly disabling in many patients as the illness evolves. In order to characterise and quantify the abnormalities a careful examination of the musculoskeletal system is an important component of the neurological examination. This cross-sectional observational study provides an overview of the typical postural deformities encountered in Parkinson's disease.

The phenomenology of postural abnormalities in PD, their impact on quality of life and factors influencing their severity have been evaluated.

## *Methods*

### Objectives

To address the following hypotheses:-

1 - Camptocormia in PD denotes significant flexion of the thoracolumbar spine and is a reversible postural deformity, present only when patients stand and walk, abating in the supine position.

2 - Pisa syndrome describes lateral trunk flexion and is often used to describe a postural deformity that can be almost completely alleviated by passive mobilisation or supine positioning.

3 - The direction of lateral flexion deformity in Pisa syndrome and mixed deformity is contralateral to the predominant PD side in those with asymmetry of disease.

4 - Severity of postural deformity affects quality of life and activities of daily living in patients with PD.

5 - Severity of postural deformity is affected by age, gender, the duration of the deformity, the duration and severity of parkinsonism, and a higher axial akinetic rigidity subscore on the UPDRS III.

## Study design and patient selection

The study was cross-sectional and observational. Patients were selected from specialist Parkinson's disease clinics at the National Hospital, Queen Square and were also invited to register their interest via Parkinson's UK and if deemed an appropriate candidate, arrangements were made for them to attend a research appointment. PD patients considered to have an abnormality of posture according to specific criteria were invited to take part. Recruitment for the study ran from July 2010 until December 2011. Research ethics were obtained from the Central London REC 2 (Bloomsbury), REC reference number 10/H0713/41. The study was registered with the UCL/UCLH/RF Joint Biomedical Research unit (UCLH site), project ID: 10/0107.

### Inclusion and Exclusion criteria

Patients had to have a diagnosis of PD according to the QSBB criteria (Gibb and Lees, 1989). Patients with atypical parkinsonism were not included in this study. Only those able to give informed consent were included.

Patients with postural deformity developing at or after the onset of PD were invited to participate. Camptocormia was defined as >/=$45^0$ thoracolumbar flexion (TLF), Pisa syndrome as >/= $10^0$ lateral flexion (LF). Patients with milder abnormalities of posture, i.e. not meeting the criteria for either Pisa syndrome or camptocormia but with TLF >$15^0$ or clinically abnormal spinal curvature in the coronal plane suggestive of

underlying scoliosis (i.e. with unequal shoulder heights or knee flexion or a laterally tilted pelvis) were also invited to take part. Those with a known diagnosis of rheumatologic or orthopaedic disorder giving rise to their abnormal posture were excluded (this included those with known vertebral collapse due to osteoporosis or myelomatous disease, those carrying a diagnosis of rheumatoid arthritis or anyone with a diagnosis of ankylosing spondylitis or other seronegative arthropathy).

## Study elements

### Clinical history and quality of life

Participants completed three questionnaires regarding their quality of life: PDQ-39 (Peto et al, 1995), WHO Well-Being Index (1998 version) (World Health Organization, 1998), the Fatigue severity scale (Krupp et al, 1989) and a postural deformity in PD questionnaire specifically formulated for this study (Table 2). The Postural Deformity in PD Questionnaire (PDinPDQ) was developed to focus on the Parkinson's patient's perception of their posture and its related impact on various aspects of their life in order to better understand which attributes of this disabling complication are most important to patients (total score ranged from a minimum of 0 to a maximum of 28).

| | Never | Occasionally | Sometimes | Often | Always |
|---|---|---|---|---|---|
| I have an abnormal posture | | | | | |
| I have great difficulty correcting my posture by myself | | | | | |
| My posture makes it difficult to maintain eye contact with others (look up) | | | | | |
| My posture limits my walking | | | | | |
| My posture is associated with pain | | | | | |
| My posture causes me to avoid social situations | | | | | |
| Thinking about my posture makes me depressed | | | | | |

**Table 2: Postural deformity in Parkinson's disease questionnaire**

Instructions: The following questions ask about how your posture interferes with your daily life, please select the most appropriate response for the statements (Never 0, Occasionally 1, Sometimes 2, Often 3, Always 4).

At the research appointment each participant underwent a thorough review of their past medical, surgical, and current medical conditions. Information sought included history of PD, medications used and history of abnormal posture. Patients were also asked to rate their pain on a visual analogue scale and cognition was assessed using the Montreal Cognitive Assessment (MoCA)(Nasreddine et al, 2005) and the Frontal Assessment Battery (FAB)(Dubois et al, 2000).

The Levodopa equivalent dose (LED) was calculated for each anti-Parkinsonian medication and the Levodopa equivalent daily dose (LEDD) for all PD medication was totalled for each patient according to published formulae (Tomlinson et al, 2010).

### Movement disorder, Neurological & Musculoskeletal examination

On the day of the assessment, patients were asked to attend having omitted their morning PD medications and having had only a light breakfast. All but 4 patients were able to attend the research appointment without taking prior medication. The MDS-UPDRS (Goetz et al, 2008) was assessed in 22 patients in the 'off' state (i.e. >12 hours following their most recent dose of medication) and in the remaining 4 patients note was made of their clinical state ('on' or 'off') and timing of medication prior to UPDRS assessment. Examination in the 'on' state following levodopa challenge was also performed in these 22 patients and response to levodopa is described in the following chapter. Each patient was then examined according to the protocol (Appendix I) which incorporated musculoskeletal, orthopaedic and neurological examination. In most cases patients also consented for photographs to be taken to document their posture and short video clips of their posture when walking.

Posture was initially assessed with patients standing and the main clinical deformity and its accompaniments noted. In the sagittal plane any flattened or exaggerated lordoses and/or kyphoses were noted. The angle of thoracolumbar flexion (TLF) was measured using an iPhone application goniometer (Yong Li, Angle protractor version 1.0, 2010, retrieved from http://itunes.apple.com/) which measured the angle of forward truncal deviation from the vertical. The angle and direction of lateral trunk flexion (LF) was also measured using the iPhone application goniometer (Figure 4). Both TLF and LF

were measured twice. The ‘usual’ standing posture that felt normal and comfortable and reflected the typical posture adopted by the patient the majority of the time, and then the ‘best’ standing posture following a command to stand up as straight as possible without aid or support. The mean of these two values was used to determine the typical angle for TLF and LF for each patient based on an assumed variation in angle throughout the day (patients often reported themselves best first thing in the morning but deteriorating by the end of the day).

Observation was made for unequal shoulder heights, pelvic tilting and asymmetry of knee flexion. The paraspinal muscles were examined for atrophy, active spasms and abnormal muscle consistency (‘wooden muscles’). Any sensory *gestes* or particular manoeuvres employed by patients to improve their standing posture were noted. Patients were also examined seated and walking. Reversibility of anterior flexion deformity was defined by the patient’s ability to lie supine with no more than one regular pillow to support their head and with their hips and knees fully extended. Reversibility of lateral flexion deformity was designated if the head came back to the midline when supine. Hip flexion deformity was assessed by Thomas’ test and knee flexion contractures were also sought. Full power testing including neck flexion and extension strength was examined and Beevor’s sign sought. In those patients able to lie prone further observation of spinal alignment was made and trunk and hip extension strength was tested.

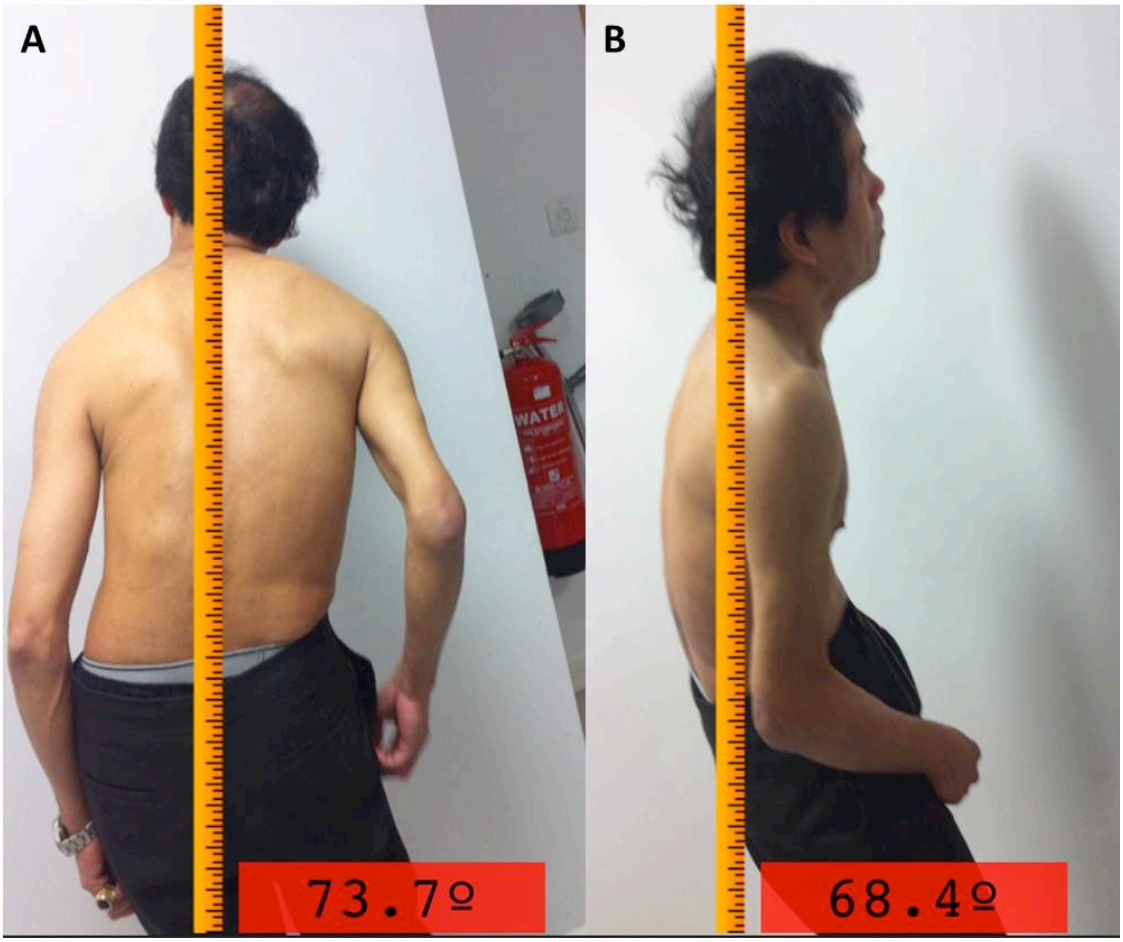



**Figure 4: Clinical measurement of lateral and thoracolumbar flexion**

Lateral flexion in the coronal plane (A) and thoracolumbar flexion in the sagittal plane (B) as measured using the iPhone goniometer application. Measurements were taken from the true vertical ($90^0$) giving lateral flexion of $16.3^0$ in (A) and thoracolumbar flexion of $21.6^0$ in (B).

## Posture Severity Score

Given the variety of postural deformities examined (sagittal, coronal, mixed), a general objective measure of severity of posture was created using various elements of the musculoskeletal examination. It incorporated 8 elements including both thoracolumbar and lateral flexion when standing, reversibility of posture when seated and supine, the presence or absence of hip flexion deformity, knee flexion deformity, inequality of shoulder heights and lateral pelvic tilting in the standing position. This was calculated following examination of the patient in the 'off' state. A maximum score of 14 indicated the most severe posture and a score of 0 the least severe (Table 3).

| Element | Score | | | | |
|---|---|---|---|---|---|
| TLF grade | $<15^0$=0 | $15^0$-$30^0$=1 | $31^0$-$45^0$=2 | $46^0$-$60^0$=3 | $>60^0$=4 |
| LF grade | $<5^0$=0 | $5^0$-$10^0$=1 | $11^0$-$20^0$=2 | $21^0$-$30^0$=3 | $>30^0$=4 |
| Postural deformity seated | Alleviated 0 | Persistent 1 | | | |
| Postural deformity supine | Alleviated 0 | Persistent 1 | | | |
| Hip flexion deformity | Absent 0 | Present 1 | | | |
| Knee flexion deformity | Absent 0 | Present 1 | | | |
| Lateral Pelvic tilt | Absent 0 | Present 1 | | | |
| Unequal shoulder heights | Absent 0 | Present 1 | | | |

**Table 3: Posture severity score**

An objective measure incorporating thoracolumbar and lateral flexion, asymmetry of shoulder heights and pelvic tilt, reversibility of posture, hip and knee flexion deformity, which can be used to assess severity of any postural deformity of the trunk (0-14).

## Parkinson's subtype analysis

PD is sometimes subdivided clinically into tremor-dominant (TD), 'postural instability and gait disorder (PIGD)-dominant', axial-dominant or akinetic rigid subtypes. These subtypes can be assigned based on cumulative scored elements from the UPDRS parts II and/or III (Jankovic et al, 1990, Schrag et al, 2000). At the time of this study design there were no defined elements from the new MDS-UPDRS to correlate with the above mentioned subtypes, so modification of those taken from the original UPDRS was performed in order to provide sub-scores for the patients in the study. For the tremor score, items 3.15 (postural tremor), 3.16 (kinetic tremor), 3.17 (rest tremor) & 3.18 (constancy of tremor) were added together (10 elements, cumulative score ranging from 0-40). For the akinetic-rigid-axial score, items 3.1 (speech), 3.3 (neck rigidity), 3.9 (arising from a chair), 3.10 (gait), 3.11 (freezing of gait), 3.12 (postural stability) & 3.13 (posture) were combined (7 elements, 0-28). For the akinetic-rigid-appendicular score, items 3.3 (limb rigidity), 3.4 (finger tapping), 3.5 (hand movements), 3.6 (pronation-supination hand movements), 3.7 (toe tapping), 3.8 (leg agility) were added (14 elements, 0-56).

Tremor and PIGD variant phenotypes have now recognised designations based on updated MDS-UPDRS calculations (Stebbins et al, 2013)

## Measures of asymmetry of parkinsonism

A previously published formula (based on the UPDRS) was modified to produce an asymmetry score (Espay et al, 2005, Espay et al, 2006). The asymmetry score was calculated as the difference between the motor deficits derived from the sum of items 3.3 (limbs only) - 3.8, and 3.15 - 3.17 (limbs only) restricted to one side, and the sum of those items from the opposite side using the MDS-UPDRS derived measurements. The greater the asymmetry score the more asymmetrical the parkinsonian motor features (e.g. R lateral score 21, L lateral score 18 = asymmetry score of 3). The predominant PD side was then assigned based on the side of higher lateral score.

## Statistical methods

The means results from the study group as a whole were calculated and then the means of the groups were also calculated and tabulated. Comparison between the three main groups or the six subgroups utilized various statistical tests depending on the type of variable in question. Comparison or correlation of nominal or categorical variables utilized Pearson's chi-square or Fishers exact tests, ordinal and non-normal quantitative data was analysed with the Kruskal-Wallis test and normally distributed quantitative data was analysed using analysis of variance (ANOVA). When investigating correlation between disease features and posture severity, linear regression analysis was used. Factors deemed possibly contributory to severity of posture were initially assessed individually with regard to any relationship with postural severity. This was done by plotting each factor in turn against the posture severity score on a scatter plot and performing correlation analysis using Pearson's or Spearman's rho correlation tests as appropriate. In each model the residuals plot and constant of variance was checked to ensure assumptions were fulfilled. Only those with significant correlations individually were included in the final multiple linear regression model. A cut-off at $p=0.15$ was selected for inclusion into the multiple regression model based on the exploratory nature of this study. In this model assumptions were fulfilled based on the residuals being normally distributed. SPSS version 19 was used for all statistical analyses.

*Results*

## Postural deformity subtypes

Examination of the 26 patients revealed a wide variety of deformity which was subdivided according to both currently recognised definitions and proposed cut-off points. Patients were grouped according to whether they had deformity in the sagittal plane alone, deformity in the coronal plane alone or deformity in both planes (mixed deformity). Table 4 illustrates the main groups, how they were defined and the subgroups.

Group 1 included those with deformity only of the sagittal plane, patients with at least $30^0$ thoracolumbar flexion (TLF) and minimal lateral flexion ($<10^0$). Group 1 was then subdivided into Subgroup A (those meeting the definition of camptocormia, i.e. severe forward flexion, TLF$>45^0$) and Subgroup B (moderate TLF: $30^0$-$45^0$).

Group 2 included all those with deformity in both planes - 'mixed deformity', with at least $10^0$ lateral flexion (LF) (i.e. Pisa syndrome) plus at least $30^0$ TLF. Group 2 was subdivided into Subgroup C (camptocormia plus Pisa syndrome, TLF$>45^0$ & LF$>10^0$) and Subgroup D (Pisa syndrome plus moderate thoracolumbar flexion, TLF $30^0$-$45^0$ & LF$>10^0$).

Group 3 comprised those with coronal plane deformity only (LF$>10^0$ or evidence of spinal curvature on clinical examination, and TLF$<30^0$) and was divided into those Pisa syndrome (Subgroup E), i.e. LF$>10^0$, and Subgroup F (LF$<10^0$ but clinical findings of spinal curvature e.g. clear spinal curvature associated with rib or loin hump, unequal shoulder heights, lateral pelvic tilting with apparent leg length discrepancy).

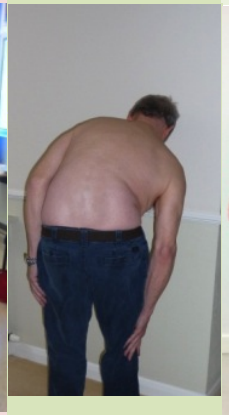
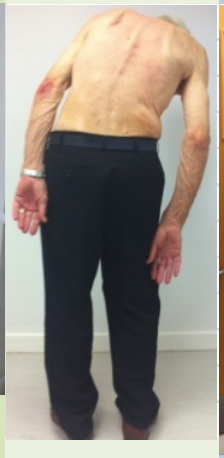
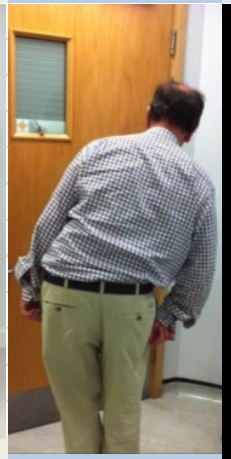
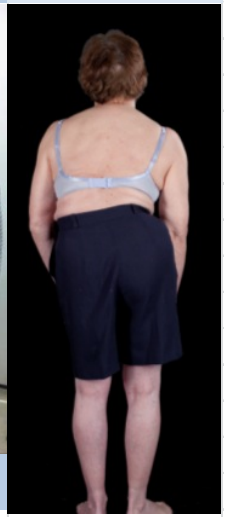
| Group | 1 - Sagittal plane deformity only | | 2 - Mixed deformity | | 3 - Coronal plane deformity only | |
|---|---|---|---|---|---|---|
| Definition | >30 degrees TLF, <10 degrees LF | | >30 degrees TLF & >10 degrees LF | | *<30 degrees TLF* | |
| Subgroup | A - Camptocormia | B - Moderate TLF | C - Camptocormia & Pisa syndrome | D - Moderate TLF & Pisa syndrome | E - Pisa syndrome | F - Spinal curve without LF* |
| Definition | >45 degrees TLF | TLF 30-45 | TLF>45 & LF>10 | TLF30-45 & LF>10 | LF>10 degrees | LF<10 |
| No. of patients | 5 | 4 | 3 | 4 | 8 | 2 |
| |  |  |  |  |  |  |
| Key | TLF | Thoracolumbar flexion | | | | |
| | LF | Lateral flexion | | | | |
| | * | clinical evidence of postural deviations (e.g. scoliosis, unequal shoulder heights, tilted pelvis) | | | | |

**Table 4: Postural deformities of the trunk in Parkinson's disease**

Eight patients had camptocormia or severe anterior truncal flexion deformity as defined by $45^0$ flexion in thoracolumbar region (subgroup A + subgroup C). Five of these patients had deformity limited to the sagittal plane with no significant lateral flexion deformity or Pisa syndrome ($LF<10^0$), i.e. subgroup A. Eight patients were defined as having moderate thoracolumbar flexion, in the range of $30^0$-$45^0$ of which four also had significant deformity in the coronal plane (i.e. Pisa syndrome).

Within Group 1 significant TLF was sometimes accompanied by flexion at other locations such as exaggerated kyphosis of the thoracic spine. In others anterior spinal curvature throughout the length of the spine (i.e. including but not limited to the thoracolumbar region) was noted. Eight patients from groups 1 & 2 had flexion limited to the thoracolumbar region with a relatively straight spine devoid of excessive kyphoses elsewhere.

Fifteen patients met the criteria for Pisa syndrome, eight of which did not have significant sagittal plane deformity and could be described as having pure Pisa syndrome. An additional two patients were studied who had significant impairment of spinal alignment in the coronal plane on clinical observation although they did not flex significantly laterally or anteriorly.

The mean posture severity score is given according to subtype in Figure 5. As expected, those with significant deformity in both planes scored the highest (subgroup C, followed by subgroup D). Camptocormia alone was graded as more severe than Pisa syndrome alone. The lowest score was for those with spinal curvature or sequelae of it (e.g. lateral pelvic tilting) but no significant deformity in either plane (subgroup F).

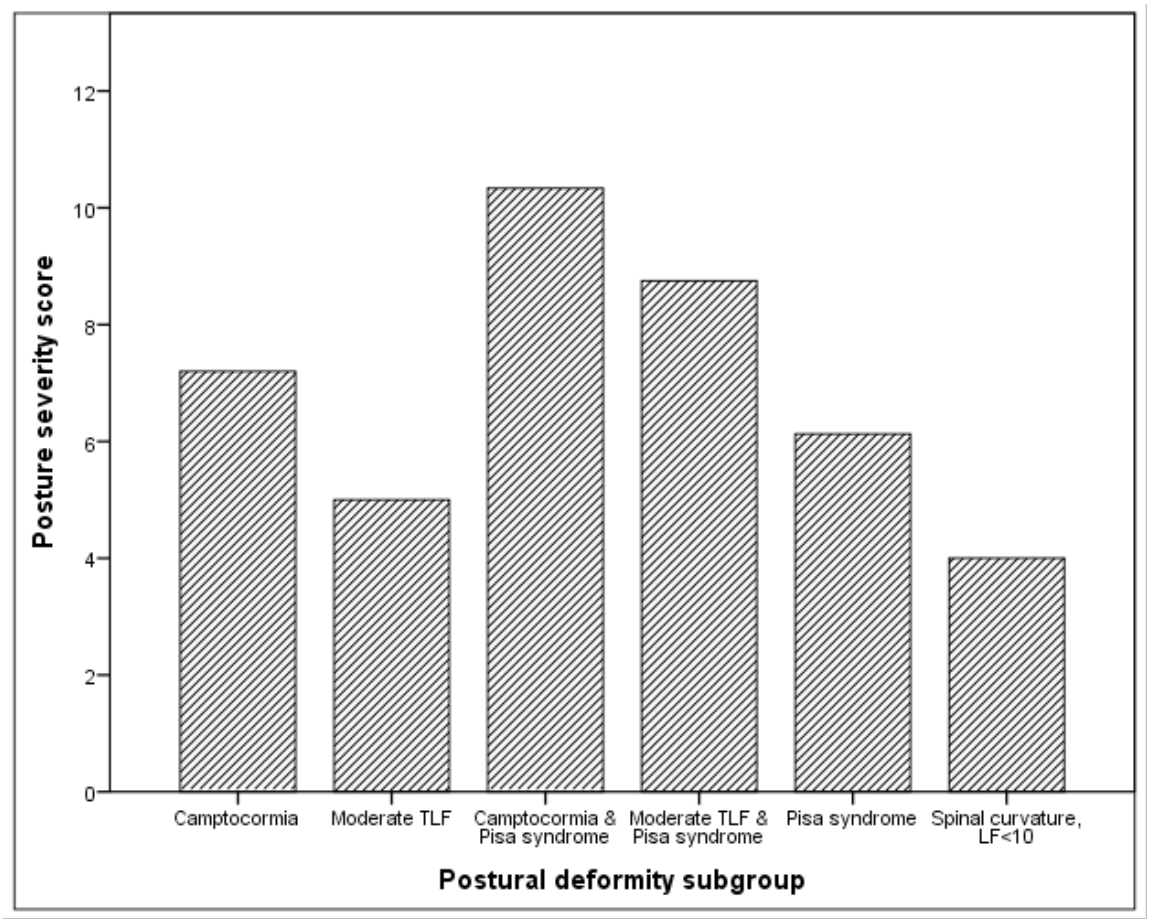



**Figure 5: Posture severity score according to subgroup**

Those with mixed deformity scored higher than those with deformity limited to either the sagittal or coronal plane.

## Clinical features

The mean age of the patients at the time of study was 71.6 years (range 63-82 years). The patients' age at perceived onset of parkinsonian symptoms was 57.7 years with diagnosis of PD being made at an average 60 years. Mean age at onset of postural deformity was 66.3 years and duration of deformity at the time of study was 5.3 years (range 0.6-13 years). There were 19 males and 7 females in the study. The mean patient age, PD duration and duration of deformity did not differ between the groups. All but five patients were of white British ethnicity, the remainder originally hailed from Cyprus, the Philippines, India, Pakistan and Poland. Two patients in each deformity group had a first, second or third degree relative with PD but none carried a known PD gene.

This data is tabulated in Table 5.

| | All Postural deformity patients with PD | Group 1 - Sagittal plane deformity only | Group 2 - Mixed deformity | Group 3 - Coronal plane deformity only |
|---|---|---|---|---|
| Number of Patients | 26 | 9 | 7 | 10 |
| Age (yrs) | 71.6 (5.3, 63-82) | 72.7 (3.6, 68-78) | 71.6 (6.3, 65-80) | 70.8 (6.1, 63-82) |
| Male: Female | 19:7 | 6:3 | 6:1 | 7:3 |
| PD (yrs) | 13.9 (5.6, 7-27) | 13.2 (4.6, 7-21) | 15.1 (6.9, 7-27) | 13.7 (5.8, 7-25) |
| Deformity (yrs) | 5.3 (2.8, 0.6-13) | 4.9 (2.9, 1-10) | 6.7 (3, 4-13) | 4.7 (2.5, 0.6-9) |
| LEDD (mg) | 1015 (336, 440-1697) | 1015 | 1087 | 964 |
| LEDD from DA (%) | 25.7 (16, 0-55) | 27.8 | 22.7 | 25.9 |
| L-dopa (yrs) | 8.6 (5.3,1.5-21) | 6.1 | 8.4 | 10.8 |
| DA (yrs) | 7.4 (3.8, 0.5-17) | 6.9 | 7.9 | 7.4 |
| DA at deformity (%) | 88.4 | 88.9 | 85.7 | 100 |
| L-dopa at deformity (%) | 69.2 | 55.6 | 71.4 | 88.9 |
| Osteoporosis | 2 | 2 | 0 | 0 |
| Chronic back pain* | 13 | 6 | 6 | 1 |
| Sciatic pain | 2 | 0 | 1 | 1 |
| Chest/Abd/Pel surgery | 14 | 4 | 4 | 6 |
| Large joint surgery | 3 | 3 | 0 | 0 |
| TLF angle ($^0$)** | 34.5 (18, 6-90) | 48.3 | 39.2 | 18.9 |
| LF angle ($^0$)** | 12.5 (8, 0-25) | 3.2 | 17 | 14.9 |
| PSS (0-28)* | 6.9 (2.3, 3-12) | 6.2 (1.9, 3-9) | 9.4 (1.3, 8-12) | 5.7 (1.6, 3-8) |
| PDQ-39 (0-156) | 68 (22, 20-116) | 70 | 72 | 63 |
| WHO well-being (0-25) | 13 (5, 3-25) | 12 | 12 | 13 |
| PDinPDQ (0-28) | 20 (5, 7-28) | 20 | 21 | 19 |
| Fatigue scale (0-63) | 39 (15, 0-63) | 32 | 42 | 43 |
| Pain VAS (0-10) | 4 (2, 0-8) | 5 | 4 | 4 |
| MoCA (0-30) | 24.1 (4.2, 10-30) | 26.3 | 23.6 | 22.7 |
| FAB (0-18)** | 14 (3.6, 6-18) | 16.8 | 14.4 | 11.9 |
| UPDRS II 'off' (0-52) | 24 (8, 0-38) | 24.5 | 27.3 | 21.1 |
| UPDRS III 'off' (0-132) | 45 (10, 27-62) | 47.3 | 40.3 | 44.4 |
| Tremor score (0-40)** | 7.3 (4, 1-14) | 9.9 | 4.3 | 6.4 |
| Axial AR score (0-28) | 11 (2, 7-15) | 11 | 12.2 | 10 |
| Lateralised score (off) | 4.6 (4, 0-14) | 6.11 | 2 | 5 |

**Table 5: Clinical features of patients with postural deformity**

Demographic, medication use, co-morbidities and examination findings in the study group as a whole and separated according to deformity group (data in brackets denotes standard deviation, range). There was a significant difference between the groups with regards to reports of chronic back pain, measured TLF & LF angles, Posture severity score (PSS), Frontal Assessment Battery (FAB) and tremor score.

(Key: *$p<0.01$, **$p<0.05$, AR Akinetic Rigid)

*Camptocormia*

This patient had been diagnosed with PD at age 63 after presenting with quivering of the fingers of his left hand and left elbow stiffness. At age 65 he developed an abnormally flexed posture of relatively sudden onset. He could recall a specific occasion when walking and feeling the sudden need to sit down because he no longer had the strength to stand upright and felt his abdomen pulling him down. There had been no incipient trauma, acute back pain or recent injury. Following that episode he described flexion of his spine every time he walked, getting worse the further he went associated with discomfort in his lower back and abdominal wall. He was taking ropinirole 3mg *tds*.

At review 6 months later and despite the addition of levodopa (co-careldopa 600mg/day) and physiotherapy, his bent spine remained unchanged. It was associated with low back discomfort which eased when he sat or lay down, but pain was not the limiting factor for maintaining an erect posture; he described when standing tall having a feeling of collapsing. He continued to feel tightness in his anterior abdominal wall muscles when he was flexed forward but no longer described a feeling of being pulled. On examination his spine flexed soon after starting to walk and became worse as he tired. There were no flexion jerks. He was able to stand upright when leaning his back against the wall. He received bilateral rectus abdominis (RA) injections (200 units of *Dysport* (Botulinum toxin type A) each side), but this did not result in any reduction of his camptocormia after 3 months. The injections were then repeated using larger doses of toxin and included injection of the hip flexors (300 units to each RA, 100 units to both iliopsoas). On repeat assessment after a 3 month interval there had been no benefit but he reported weakness when sitting up from bed. A last attempt was made treating only the iliopsoas (200 units each side) due to the finding of hip flexion tightness but again this made no impact on the flexed posture.

On examination his TLF angle was $55.6^0$. He was unable to extend his trunk from the prone position, but there was no evidence of muscle weakness elsewhere and Beevor's

sign was absent. There was bilateral hip flexion tightness and a fixed knee flexion deformity on the left. Physiotherapy assessment showed he had a weak core (abdominal muscles predominantly) and tight shortened hip flexors (L>R) on the modified Thomas test. He was shown and advised to perform twice weekly hip flexor stretches, and how to use the wall to practice standing tall.

Six months later there was no improvement and he now complained of visual limitation – he could not look someone in the eye during conversation and had recently started esomeprazole for symptoms of gastro-oesophageal reflux, both probably indirect consequences of his severely flexed posture (Video 1). He was assessed by a spinal deformity surgeon but decided against spinal fixation. He was able to walk half a mile with a wheeled frame. He was still able to lie flat when supine but could not bring himself upright even by walking his hands up a wall. He had thin paraspinal musculature and there were no active spasms or spontaneous contractions of rectus abdominis on palpation. There was fixed flexion deformity affecting both knees. He was admitted for intensive in-patient physiotherapy during which attempts were made to improve his posture but the benefits were short lived. The following year his posture appeared much worse, he walked with $>90^0$ of thoracolumbar flexion and was unable to sit upright in the chair without supporting himself with his elbows. It appeared that further flexion of posture was limited by the proximity of his ribcage to his pelvis. He used a seat-belt adapted chair during meals in order to free his arms to feed himself safely in an upright position.

*Coronal plane deformity*

This 72 year old female PD patient had lateral flexion deformity away from her more severely affected Parkinson's side. She had noted she was starting to lean to the left about 10 years previously but could not recall a clear precipitant. Her medications at the time of onset of deformity included pramipexole and combined levodopa/carbidopa/entacapone. On examination she had $27^0$ LF to the left which improved to $18^0$ when she was asked to stand as tall as possible, but could not be maintained. Her lateral trunk flexion persisted when seated, supine, while walking and whether 'off' or 'on' medication (Video 2). Her trunk revealed a mild loin hump in the right paraspinal region with active spasm of the right thoracic paraspinals when she attempted to stand straighter. Her left hip was elevated and did not interact with her base of support, weight bearing was maximal through the right hip and her right trunk was extended and stiff. At rest the active spasms were limited to her right trapezius and sternocleidomastoid muscles which appeared to be attempting to correct her head position to the midline. There was no weakness on examination of power.

Her pramipexole was discontinued and her Pisa syndrome improved by approximately 30% but this improvement was not sustained and pramipexole was restarted as it was deemed the only medication to effectively control her tremor. She was supplied with an orthotic brace but described wearing it as intolerable. She had several injection of botulinum toxin into various sites (left external oblique, lumbar erector spinae, thoracic erector spinae) without any appreciable benefit to her posture.

Several years later her posture remains unchanged with significant lateral flexion (20-$30^0$), but despite this she remains mobile with a rollator and has not experienced increasing falls or pain.

All but 2 patients described a unilateral onset to their symptoms. Five patients reported onset of their Parkinson's with tremor, 10 with slowness and/or stiffness, 11 recalled both tremor and stiffness or slowness at onset. The range of presenting symptoms did not differ between the groups.

Two-thirds could not recall a precipitating event at the onset of their abnormal posture; in the sagittal deformity group three patients felt the onset may have been related to a recent mechanical stress such as heavy lifting or excessive exercise and one felt the postural deformity followed a prolonged period for illness after an operation. Of those with mixed deformity one patient felt it had occurred at the time of a medication change (coming off orphenadrine and diazepam – treatments for her foot dystonia) and one felt the deformity coincided with new onset leg pain. In the coronal plane deformity group three reported onset with new leg and/or back pain. Speed of onset of the deformity was described as gradual (over several months) by most patients (n=19) and subacute (over days to weeks) in six, just one patient reported onset of deformity within hours.

Eighty-eight percent (23/26) of patients were taking a dopamine agonist at the onset of their deformity, 69% were taking Levodopa and 65% were taking both. The mean Levodopa Equivalent Daily Dose (LEDD) of all anti-Parkinsonian medications was 1015mg (mean from Levodopa 662mg, mean from DA 253mg, remainder made of up of Amantadine, MAOBIs and COMTIs). The mean percentage of the LEDD from a dopamine agonist was 25.7%. There did not appear to be a difference between the different deformity subtypes in terms of dopamine agonist use at onset of deformity with the majority taking one, notably all patients with coronal plane deformity were on a dopamine agonist at the onset of their deformity. Of all those treated at some stage with a dopamine agonist, the mean duration of use prior to deformity onset was 2 years (SD 5, -9 to 12). Fewer patients with sagittal plane deformity were taking levodopa when their postural abnormality became apparent (56% versus 71% in the mixed group and 89% in the coronal plane deformity group) but this did not fulfil a significant difference between the groups (Fishers exact test = 2.42, p=0.3).

All but two had seen a physiotherapist with regards to their posture, 4 had tried hydrotherapy, 6 either pilates, yoga or the Alexander technique, two-thirds had bought

over the counter back supports, 5 had received botulinum toxin therapy (none within one year of the study) and 38.5% had been supplied with bespoke orthotic spinal braces. No patient felt that any single therapy had significantly improved their posture. A third of patients felt they were unable to improve their posture by any means, two-thirds described that by using furniture or walking aids they could straighten up somewhat.

The mean score on the PDinPDQ was 20/28 (SD 4.7, range 7-28). This correlated with quality of life as measured using the PDQ-39 ($R^2$ linear = 0.37, Pearson's correlation 0.61, p=0.001) and the WHO well-being index ($R^2$ linear 0.21, Pearson' correlation -0.46, p=0.019). The PDinPDQ focussed on the elements of posture that were subjectively most severe for the patient, the factor being most implicated was the effect of abnormal posture on walking, followed by difficulty making eye contact. There was no significant difference between those with sagittal plane deformity, mixed deformity or coronal plane deformity in relation to quality of life as measured by the PDQ-39, the WHO well-being index, the PDinPDQ, self-reported fatigue or pain measured using a visual analogue scale (VAS). Cognition as measured using the MoCA did not differ between groups but the frontal assessment battery did. The mean FAB score was 14/18 (SD=3.6) and in the 3 different groups the means were Group 1 (sagittal plane deformity only) FAB = 16.8; Group 2 (mixed deformity) FAB = 14.4; Group 3 (coronal plane deformity only) FAB = 11.9. The Kruskal-Wallis chi square test was significant beyond the 0.05 level: chi square (2) = 7.26; $p<0.05$ therefore rejecting the null hypothesis of equality of medians between the three groups.

Only 2 patients had received a formal diagnosis of osteoporosis and were taking bisphosphonate medication at the time of study and those patients both fell into the camptocormia group. None of the patients had received or were currently taking neuroleptic or central anticholinesterase inhibitor medication. Half of the patients in the study complained of chronic back pain and this differed significantly between the groups (Fishers exact test = 10.9, $p<0.01$). Two-thirds of group 1 patients and 6/7 patients in group 2 complained of back pain whereas only 1 patient with coronal plane deformity complained of back pain. On the other hand sciatic-type pain was a complaint in only two patients – both of which had coronal plane deformity. Despite that, pain was not the major complaint from patients and pain as measured by VAS did not differ

between groups with a mean of 4/10.

Previous surgical procedure to abdomen, pelvis or chest was common in all groups, 14/26 study patients. This included laparoscopy, colectomy, hysterectomy, mastectomy, cholecystectomy, prostatectomy and inguinal and umbilical hernia repair. Three patients in group 1 had previously undergone large joint surgery (e.g. total hip or knee replacements), none in the other 2 groups had.

On examination none of the patients had dystonia (posturing with jerks or tremor, active spasms or contractions associated with the abnormal posture, or sensory *gestes*). Tightness of rectus abdominis was present in two patients with sagittal plane deformity while standing, but this was not accompanied by jerking or witnessed 'pulling' movements. Limb weakness and Beevor's sign was absent. Rib or loin humps were present in 20-29% of patients within each group, unequal paraspinal muscle bulk was evident in 4 of the cases with Pisa syndrome and in the relatively hypertrophied side there was a wooden consistency on palpation. A fixed knee flexion deformity was found in a third of patients. Tightness of hip flexion was invariably present in those with sagittal plane deformity and two patients had hip flexion deformities on performing the Thomas test. Almost half of patients were unable to perform or had impaired trunk extension from the prone position, one quarter performed it normally and the remainder were too frail to lie prone on the examination couch. This was notably difficult for those patients with sagittal plane deformity only, of which 75% were unable to extend their trunk from the prone position. Severity of posture as scored by the MDS-UPDRS III item 13 was scored as moderate in a quarter of patients and severe in three-quarters.

The mean posture severity score (PSS) in the patients was 6.88 (SD 2.2, range 3-12). A correlation was found between PSS and MDS-UPDRS II, $R^2$ linear = 0.33, Pearson's correlation = 0.58 ($p=0.01$), but correlation was not found between posture severity and MDS-UPDRS III.

## Reversibility of postural deformity

Of the 5 patients with camptocormia full clinical reversibility of anterior spinal flexion when supine was possible in 3, but this was not a simple matter of lying flat and the abnormal posture resolving immediately – these patients all took time in resting their head back on the couch. In those with moderate TLF (subgroup B) anteriorly flexed posture abated fully in just 2. In the sagittal plane deformity group as a whole (subgroup A & B) three patients had knee flexion deformity and two had both fixed knee and hip flexion deformity evident on supine examination (Figure 6). One had fixed curvature of his thoracic spine restricting his ability to lie flat suggestive of coincidental ankylosing spondylitis. In all those without full clinical reversibility there was evidence of skin irritation in the creases of the abdominal wall flexed segment when they lay supine. There is therefore clinical evidence of deformity persistence in the supine position in the majority of studied patients with camptocormia and moderate thoracolumbar flexion deformity.

**Figure 6: Persistence of deformity in camptocormia**

This patient has persistent abnormality of posture on supine positioning, including hip and knee flexion contractures, limiting his ability for full extension when recumbent.

Only 37.5% (3/8) patients had resolution of lateral flexion when supine. Figure 7 depicts persistence of lateral flexion in a patient with Pisa syndrome on supine positioning. There were no hip flexion deformities in the coronal plane deformity group and knee flexion deformity was present in only one.

None of those with mixed deformity had reversibility of both anterior and lateral flexion deformities when supine.

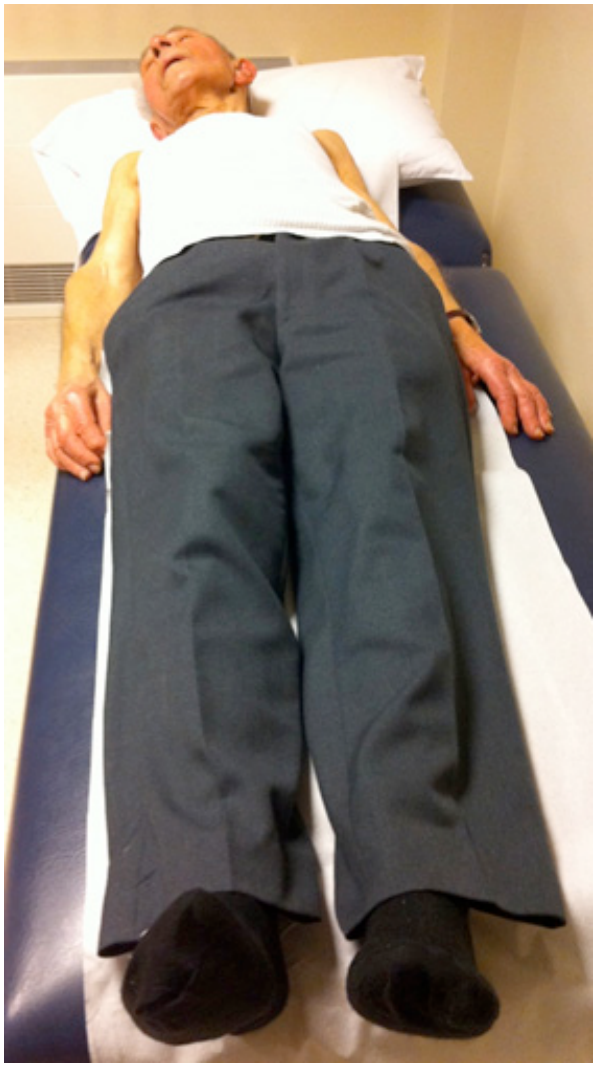


**Figure 7: Persistence of deformity in Pisa syndrome**

This patient had persistent lateral flexion deformity when recumbent and a tilted pelvis as suggested by his apparent inequality of leg length.

## Direction of lateral deformity and predominant PD side

Asymmetry of Parkinson's disease defined by an absolute lateralised score equal to 5 or greater (difference in R and L UPDRS points) as a cut of value of asymmetry (Uitti et al, 2005) showed the majority of patients with lateral flexion deformity deviating away from their predominant symptom side (81%) and exhibited a trend between direction of lateral deviation and predominant PD side (Fisher's exact test p=0.061):-

| | | Predominant PD Side | |
|---|---|---|---|
| | | Right | Left |
| Direction of lateral deviation | Right | 2 | 5 |
| | Left | 4 | 0 |

Advancing the cut off for asymmetrical disease to >5 there was 100% concordance of patients tilting contralateral to the predominant PD side (Fisher's exact test p=0.029) but only 7 patients displayed this degree of asymmetry:-

| | | Predominant PD Side | |
|---|---|---|---|
| | | Right | Left |
| Direction of lateral deviation | Right | 0 | 4 |
| | Left | 3 | 0 |

## Factors associated with severity of deformity

Postulating that severity of posture would be affected by age, gender, the duration of the deformity, the duration of parkinsonism, severity of parkinsonism and a higher axial akinetic rigidity subscore on the UPDRS III (indicating an axial predominant akinetic rigid phenotype), each factor was assessed individually to determine if there was a relationship with severity of posture (PSS).

Age

A linear relationship was not observed when age was plotted against PSS. Age was then recalculated as a categorical variable. The median age being 70.7 years, a cut off of <71 or >71 was used to compute a new categorical age variable. This was then entered as a factor in the linear regression model but it remained a non-significant factor (Beta coefficient =0.06, p=0.95).

Gender

There were 19 males and 7 females and the males had an on average higher PSS than females (7.2, 6.0 respectively), but according to the model there was no significant correlation (Beta = -1.21, p=0.23).

Duration of PD

A linear relationship was demonstrated between PSS and duration of parkinsonism ($R^2$=0.07), in the regression model this showed a correlation of Beta=0.1, p=0.2 (this was outside the stipulated cut-off and was therefore not included in the final model).

Severity of PD

Severity of PD as measured using the UPDRS III with patients 'off' was graphed against PSS but no linear relationship was demonstrated. The median score was 45.5 (range:27-62) and this was used as a cut-off to categorise into those with a score >45.5 and those with one <45.5. This gave 2 groups, the UPDRS III >45.5 group having a

mean PSS of 6.8 and UPDRS III <45.5 group having a mean PSS of 6.9. In the general linear model there was no significant correlation (Beta=-0.09, p=0.93).

Duration of deformity

A positive linear relationship was demonstrated when PSS was plotted against duration of deformity ($R^2$=0.1). The linear regression found a strength of association of Beta=0.25, p=0.115 within the set criteria for accepting into the multiple regression model.

Axial predominant PD

A linear relationship was demonstrated between the axial akinetic rigid subscore (assimilated from the UPDRS III) and the severity of posture ($R^2$=0.25). In the linear regression this was found to be a significant correlating factor (Beta=0.46, p=0.02) and so was also entered into the final multiple regression model.

Both axial akinetic rigid subscore and duration of deformity were therefore included in the final multiple linear regression analysis. The influence of each factor and their measures of certainty were as follows: axial akinetic rigid subscore Beta = 0.70 (p=0.002, 95% CI: 0.29-1.02), duration of deformity Beta = 0.47 (p=0.023, 95% CI: 0.07-0.86). The resulting model was significant (p=0.005) and 43% of the variability in severity of posture was explained by the axial akinetic rigid subscore and the duration of deformity (R-squared = 0.432).

## *Conclusion*

This study has shown that there is an extensive range of postural deformities in PD, ranging from the pure camptocormia - the severe expression of anterior thoracolumbar flexion - to the severe listing of Pisa syndrome deformity. The standard definition of camptocormia as a fully reversible deformity when recumbent does not take into account secondary hip and knee flexion contractures, excess thoracic kyphosis or disproportionate antecollis, all of which may limit supine positioning. A more suitable definition might therefore read 'camptocormia may abate considerably in the supine position, but hip and knees flexion contractures and difficulty extending the neck fully may limit full extension when recumbent'. Those patients with fixed anterior spinal flexion when supine should be investigated for co-incident rheumatologic disease. Similarly in Pisa syndrome patients supine positioning infrequently resulted in resolution of lateral flexion suggesting that aside from perhaps those presenting acutely, this deformity is also not necessarily alleviated by the recumbent position.

In the majority of patients a clear precipitant prior to the development of abnormal posture was not recalled, but in a few there did seem to be an association with mechanical or radicular-type pain (e.g. sciatica). Only one patient described a clear temporal association of abnormal posture onset with a change to medication. This female patient recalled that shortly after being weaned off orphenadrine and diazepam (which had been started for dystonia of her left hand and foot), she noticed that her posture was significantly bent forward. Surgical procedures prior to the onset of postural deformity were common in the study group which raises the possibility that post-operative pain, immobility and altered spinopelvic alignment are possible contributors to abnormal posture development. Prolonged bed rest following operative procedures was also identified by some patients as a time when they felt their posture started to deteriorate; this may be especially true of sagittal plane deformity in those who have spent sustained periods propped up on several pillows in a flexed posture. Total hip replacement may on occasion alter spinopelvic alignment and possibly play a contributory role. Several case reports and case series have suggested that

dopaminergic medication – in particular dopamine agonists – may trigger postural deformity (Cannas et al, 2009, Cannas et al, 2005). This study was not powered to specifically investigate this question, but all patients with coronal plane deformity were noted to be taking a dopamine agonist at the onset of their deformity. In those with camptocormia and moderate thoracolumbar flexion just over half were on levodopa at onset of deformity compared with much higher figures in those with mixed or coronal plane deformity. This may reflect the historical pattern – patients with post-encephalitic and idiopathic PD in the pre-treatment era often had more severe postural deformities than are encountered today especially in the sagittal plane (Martin, 1965b, Martin, 1965a).

Abnormality of posture was the single biggest complaint from patients in the study. The severity of postural deformity correlated with MDS-UPDRS II and the activities of daily living subsection of the PDQ-39. This underlines that abnormal posture strongly impacts upon activities of daily living, is a major source of disability to the patient and a potential burden to the care giver.

Those with deformity limited to the coronal plane appeared to have worse scores on the FAB. Previously Abe et al suggested that frontal lobe dysfunction may be an important factor in the pathogenesis of camptocormia (Abe et al, 2010) with 'central fatigue' leading to difficulty sustaining attention. This is an interesting notion and the findings of this study suggest this could also be a factor in coronal plane deformity.

Active dystonia on clinical examination was not found. In a few patients with anteriorly flexed deformity the rectus abdominis was rigid to palpation and in many in both groups there was wooden consistency to the paraspinal muscles. It seems insufficient to conclude that a tense rectus abdominis when standing indicates dystonia, rather it could be a compensatory phenomenon: in a kyphotic position the forces of gravity act anteriorly to the base of support (the feet) and a counteracting force might be that of stabilizing anterior abdominal wall muscles to increase abdominal pressure and decrease the force of gravity in this position (Roussouly and Pinheiro-Franco, 2011). This woody consistency to the spinal musculature and the rib or loin humps seen in some patients likely reflects the chronicity of deformity (mean duration of deformity 5 years) with

possibly disuse of muscles resulting in loss of muscle bulk and increases in connective tissue. Clinical examination alone can be of limited value in the diagnosis of dystonia especially in complex spinal deformity, but it is also notoriously difficult to interpret the results of electromyography studies in truncal and back muscles with patients in the standing position, and various authors interpret results very differently (Spuler et al, 2010, Jankovic, 2010, Di Matteo et al, 2011, Tassorelli et al, 2012, Tinazzi et al, 2013).

Although evidence of generalised muscle weakness was not found it was observed that many patients had difficulty recruiting paraspinal muscles when asked to stand up straight, instead they would push down on one knee or hyperextend their neck in order to appear taller. When asked to extend their trunk from the prone position half the patients had difficulty or were unable to do so. This could be due to a primary or secondary myopathy (e.g. disuse), a fixed spinal pathology precluding any such movement, or that the mechanism of performing such a manoeuvre has been forgotten (apraxia, failed proprioception or loss of previous learned manoeuvre due to cortical remodelling). Wright and colleagues have studied the integration of sensory and motor inputs in the axial musculature in PD and established that accuracy of hip and trunk kinaesthesia is poor in PD patients compared to controls (Wright et al, 2010).

In concordance with many previous studies there was a tendency for asymmetric PD patients to tilt away from their predominant parkinsonian side. This tendency appeared to increase with greater limb asymmetry. In contrast to early animal studies which show complete correlation between lesion side and direction of lateral deviation, this study and many of those previously reported never show complete agreement. Reasons for this may include incorrect selection of the predominant PD side, choosing a predominant side in those with symmetric PD, change to the predominantly affected side over the course of a patients Parkinson's disease or that other external factors may affect the side that lateral flexion occurs (e.g. radiculopathy such as sciatica which may precipitate flexion in one direction to relieve an acute pain). One must also take into account that quadruped animals will behave differently than biped humans. The tendency to flex anteriorly (in the sagittal plane) does not have an animal equivalent and so the complexities of camptocormia or three-dimensional mixed deformities are not

something that can be explored in the laboratory.

Duration of deformity and high axial akinetic rigid subscore were implicated as factors contributing to severity of postural deformity in this study group. Bloch et al also reported a higher axial score when they compared 8 PD patients with camptocormia to those without (Bloch et al, 2006). Axial akinetic rigid or postural instability/gait difficulty (PIGD) subtype may therefore be a risk factor for severe postural deformity development. Severity of postural deformity also increases with time from onset. This is a very important point to emphasise because if intervention does not occur subsequent deterioration is inevitable.

# Chapter 3: Response to Dopaminergic therapy in PD patients with deformity

## *Introduction*

Postural deformities have been recognized since the early descriptions of the shaking palsy or Parkinson's disease. Initially this was recognized as an anterior stooping or a "...propensity to bend the trunk forwards" (Parkinson, 1817), while deformity in the coronal plane was first depicted by Richer's statuette of a woman with mixed or 'kyphoscoliotic' deformity (Richer and Meige, 1895). Very severe abnormalities of posture were often encountered in patients with Post-encephalitic Parkinsonism and in those with idiopathic PD in the pre-treatment era when they were described as negative symptoms of PD due to disorders of postural fixation and equilibrium or disorders of righting (Martin, 1967). Much less attention was paid to these complications following the introduction of effective drug treatments which managed the various symptoms and signs of PD, and this chronology may suggest that postural deformities are therefore dopa responsive phenomenon or a complication of long untreated parkinsonism. However in recent decades patients with severe abnormalities of posture, reminiscent (but often less severe) of those early cases have been described and despite optimisation of dopaminergic medication, posture often fails to improve. This leads to two main questions:-

1 - Is postural deformity in the setting of PD a dopa-responsive phenomenon?

Recent literature does not often describe an improvement in posture (usually camptocormia) following increase in dopaminergic therapy (Azher and Jankovic, 2005, Djaldetti et al, 1999) but no studies have actually attempted to investigate this quantitatively.

2 - Are patients with significant abnormalities of posture likely to be less levodopa responsive in general than those without a significant postural disorder?

With regards to levodopa responsiveness some authors report that patients with camptocormia are less levodopa responsive than those without but again the literature on formal studies is sparse. Bloch et al reported an improvement in UPDRS III of 28% in their 8 camptocormic patients versus 62% in the patients without camptocormia following a suprathreshold levodopa challenge (50mg more Levodopa than that usually taken to good effect in the morning) (Bloch et al, 2006) suggesting the response in the camptocormia patients was relatively modest. This small study tested a slightly higher than normal Levodopa dose – as the authors may have hypothesised that larger doses of medication would be required to combat abnormal posture than would otherwise be needed for bradykinesia, rigidity or tremor. There has not been further study on whether 'supramaximal' pharmacotherapy could improve postural deformity over and above the doses given to treat the other symptoms of PD (e.g. tremor, slowness, stiffness) but this remains an important question.

## *Clinical case – camptocormia and response to dopaminergic therapy*

This descriptive case history highlights the difficulty encountered when faced with patients with severe abnormality of posture not responsive to therapy. This patient was described in Chapter 2; below are details of attempts to improve his posture with dopaminergic medication.

A 59-year old retired solicitor had initially noticed quivering of the fingers of his left hand followed by stiffness in his left elbow. He was diagnosed with PD aged 63 and had a trial of co-beneldopa to which his tremor responded. He was switched to ropinirole 3mg *tds* for maintenance therapy and described his symptoms as stable for 5 years.

Aged 65 he developed an abnormally flexed posture. Parkinson's examination at this time revealed moderate facial hypomimia and a quiet slightly slurred speech. He had moderate micrographia and an intermittent coarse resting tremor of the left hand. There was moderate bilateral slowness of finger movements worse on the left with accompanying rigidity. He had difficulty rising from a low chair and his posture was flexed with absent arm swing and reduced steppage gait. The pull test was negative. Co-careldopa was added to his ropinirole without dramatic improvement to his posture, and he was not aware of any difference to his posture or other symptoms if he missed one or several doses. At review 6 months later despite increased levodopa (Co-careldopa 600mg/day), his bent spine remained unchanged. Co-careldopa was reduced back to 300mg/day as he reported it caused sleepiness and was of dubious benefit. He underwent focused botulinum toxin injection on three occasions without benefit. At review the following year his parkinsonism and flexed posture were unchanged and he continued on ropinirole 3mg *tds* and co-careldopa 100mg *tds*. His only complaint was of his poor posture. He attended Parkinson's exercise classes and saw a physiotherapist weekly. His ropinirole was increased and changed to an extended release preparation (12mg/day), his co-careldopa stopped.

Aged 69 years he underwent a formal levodopa challenge (250mg co-beneldopa dispersible). His baseline MDS-UPDRS III was 48 and his TLF measured at $55.6^0$ from

the vertical. One hour post challenge his TLF angle was measured at $47.1^0$ and his MDS-UPDRS III 47, he felt woozy and sleepy, but denied nausea and had no dyskinesias. This was concluded as a minimal improvement in posture and a negative levodopa challenge. Six months later examination was notable for axial rigidity and hypophonia, he was still able to lie flat when supine but could not bring himself upright even by walking his hands up a wall. Due to concern regarding onset of abnormal postures in relation to dopamine agonists it was advised he restart levodopa and come off the ropinirole, but due to a lack of response with co-careldopa and a benefit to his tremor with ropinirole he reverted to his previous regime.

The following year (aged 70, 5 years from onset of deformity and 12 years from onset of motor signs of PD) an apomorphine challenge was performed. Only a 17% improvement in MDS-UPDRS III was found to 3mg subcutaneous apomorphine hydrochloride, this was repeated using 4.5mg and again the same response occurred, there was associated yawning and sudden onset of sleep. There was no postural drop in blood pressure and no dyskinesias. Degree of improvement in TLF was again minimal with the angle measured at $62^0$ pre-challenge and $55^0$ post-challenge. This was deemed a negative apomorphine challenge, amantadine followed by selegeline hydrochloride were added to his ropinirole.

The following year his posture appeared much worse, he walked with $>90^0$ TLF and was unable to sit upright in the chair without supporting himself with his elbows. He reported feeling in general no different from the previous year but did admit his mobility had declined. He used a 3-wheeled rollator and had sustained a few falls in the preceding months. Co-Careldopa was restarted despite his previous negative challenge due to his increasingly severe posture and out of a lack of alternative options. Six months later his parkinsonism was objectively improved (MDS-UPDRS 41) and TLF was measured at $60^0$ with ability to straighten to $45^0$ with effort, but not maintain this during walking or standing. This improvement was felt to be due to his co-careldopa and he was advised to uptitrate to a dose of 600mg/day.

## *Methodology*

Hypotheses:-

1 - Postural deformities are not dopa-responsive; they do not improve following a levodopa challenge.

2 - PD patients with postural deformities are less levodopa responsive than is typical for PD patients. PD patients with camptocormia are less levodopa responsive than PD patients without this deformity.

An objective assessment of parkinsonism severity using the MDS-UPDRS III (Goetz et al, 2008) and posture (measurement of both thoracolumbar flexion and lateral flexion as described in chapter 3) was performed both before and after a levodopa challenge. The choice was given to patients whether to participate in a 'normal' or 'supramaximal' levodopa challenge. The 'normal' levodopa challenge dose was calculated as the LED of the patient's usual morning dose of medication (i.e. a dose sufficient to lead to an 'on' state), and the supramaximal challenge as 1.5 times the LED of the usual morning medication. Patients' levodopa naïve were not enrolled in the supramaximal challenge. The challenge dose was given in the form of *Madopar* dispersible tablets (one tablet = 100mg/25mg levodopa/benserazide) and the 'on' examination was performed at one hour from the time the challenge dose was given.

Twenty-two patients from the clinical study (chapter 3) took part and a further 3 patients with postural deformity according to the original inclusion criteria were recruited from clinic (subgroup 5 - 2 patients; subgroup 6 – 1 patient). Thirteen patients underwent a 'normal' levodopa challenge and 12 patients a supramaximal challenge. Mean baseline 'off' MDS-UPDRS III, posture severity score, lateral flexion and thoracolumbar flexion did not differ significantly between those receiving normal and supramaximal challenges. There was also a relatively equal spread of deformity between those receiving either type of challenge, except subgroup C (camptocormia and Pisa syndrome) in which no patients consented to a supramaximal challenge (Figure 8).

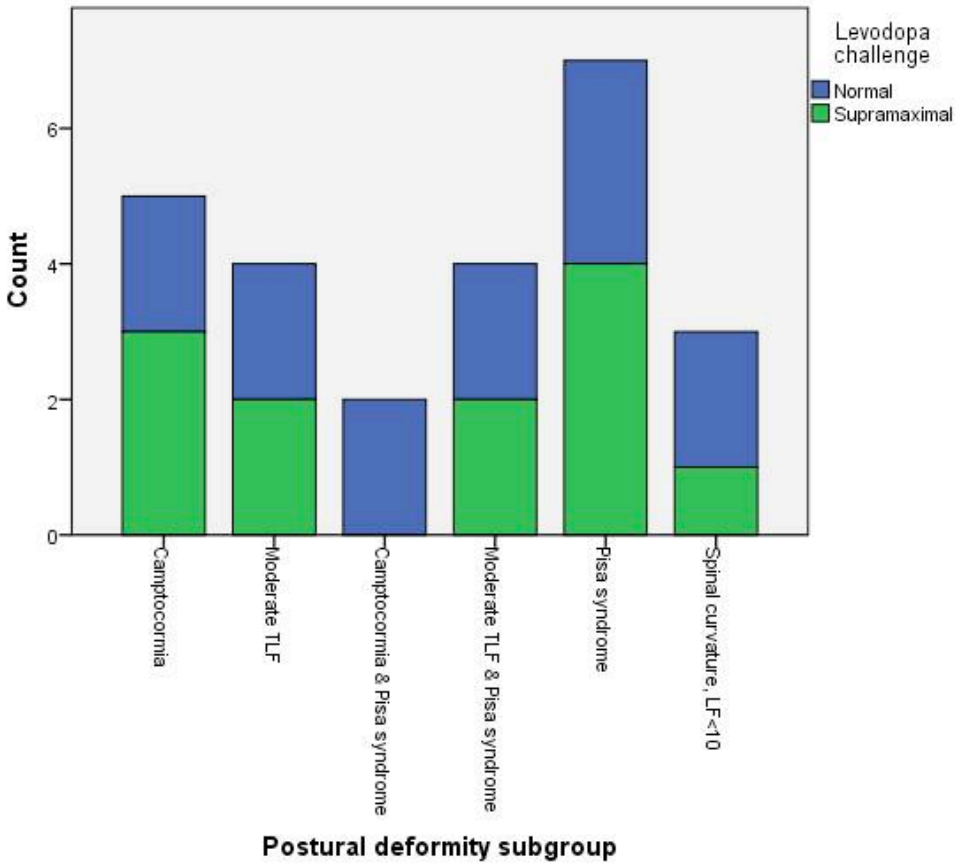



**Figure 8: Distribution of Levodopa challenge type by subgroup**

An improvement in MDS-UPDRS of 30% or greater was used to ascertain a positive challenge (Merello et al, 2002). An improvement of $5^0$ in lateral flexion and/or $10^0$ in thoracolumbar flexion was noted as a minimal improvement in posture, $10^0$ improvement LF and/or $20^0$ in TLF was deemed a moderate improvement in posture and $15^0$ LF and/or $30^0$ TLF a significant improvement in posture. A change of less than $5^0$ in either plane (either positive or negative) was considered negligible.

## Dopa-responsiveness of postural deformities

In the group as a whole LF deteriorated by $0.3^0$ following the challenge and TLF improved by just $1.8^0$. When divided into normal and supramaximal challenges, LF improved by $1^0$ (SD 3.3) in the normal challenge group and deteriorated by $2.7^0$ (SD 4.3) in the supramaximal group, TLF improved by $3.4^0$ (SD 7.7) in the normal challenge group and deteriorated in the supramaximal group by $0.4^0$ (SD 6.3).

The mean improvement in LF was negligible in all subtypes. There was a mean improvement of $1.6^0$ in those with Pisa syndrome only, but in those with mixed deformity LF deteriorated by a few degrees (Figure 9). Any change in TLF was classified as a minimal improvement in all those with camptocormia (Mean improvement in TLF: camptocormia alone $6^0$, camptocormia & Pisa syndrome $7^0$) but there was a negligible change to TLF in all other subgroups (Figure 9).

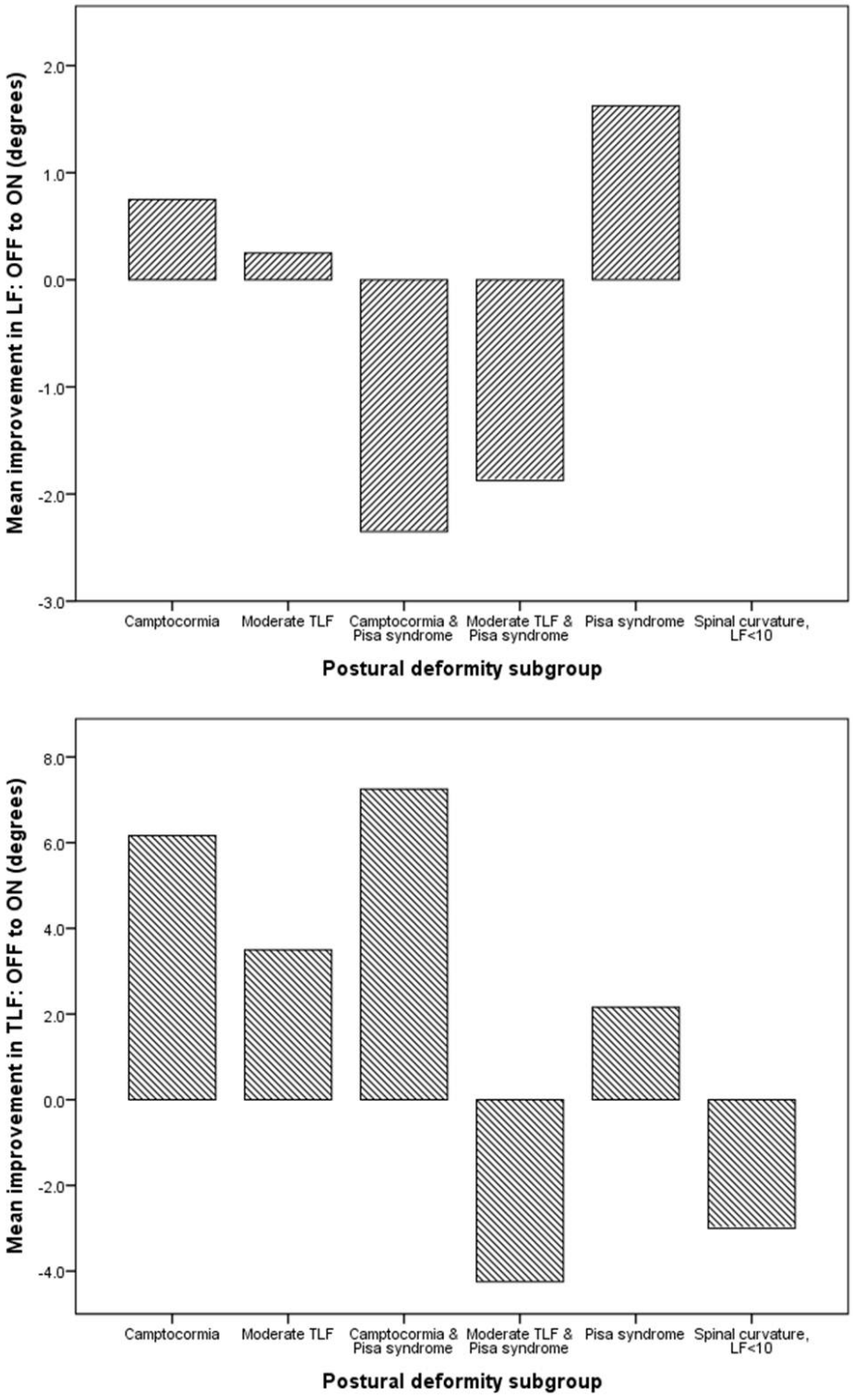



**Figure 9: Dopa-responsiveness of postural deformity in PD**

Change to Lateral flexion (top) and thoracolumbar flexion (bottom) following L-dopa challenge.

## Response to Levodopa in patients with postural deformity

Response to Levodopa challenge in the group as a whole showed a 28% (SD 22) improvement in Parkinson's motor score (MDS-UPDRS III). The mean improvement in those who underwent a normal challenge was 30% (SD 21), in those undergoing a supramaximal challenge the mean improvement in motor score was 27% (SD 23). When divided per subgroup, those with camptocormia only had a 15% improvement (n=5) (following either a normal or a supramaximal Levodopa challenge). For those with moderate TLF or mixed deformity (subgroups C and D) the improvement was approximately 30%. Pisa syndrome patients (subgroup E) improved by only 20% but those with spinal curvature and no deformity of plane improved by 62.5% (Figure 10). As the groups were small and not significantly different (Kruskal-Wallis Test p=0.126), differences in motor responses to L-dopa challenges could not be inferred across the subgroups.

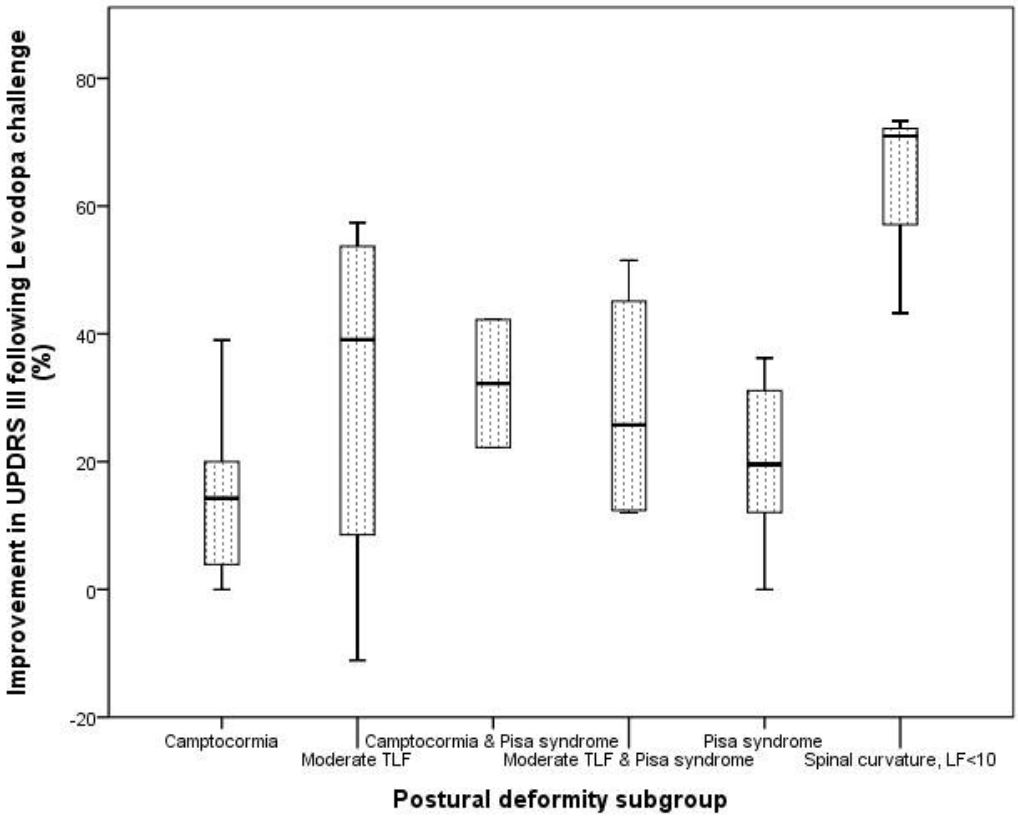



**Figure 10: Response to Levodopa in patients with postural deformity (UPDRS)**

Box plot showing improvement in UPDRS part III following Levodopa challenge according to postural deformity subgroup. The line in the middle of each box gives the median value within the subgroup, the edge of the boxes the quartiles and the whiskers the extreme scores of each subgroup.

The Hoehn & Yahr (H&Y) stage of all 25 patients was also assessed pre and post challenge. The median H&Y grade at baseline ('off') was 3 (mean 2.64) and following a levodopa challenge was 2 (mean 2.52). These repeated measures (H&Y before 'off' and after 'on') are given in table 6 and show that 88% (CI: 69%-97%) of patients had no change to their H&Y stage and the remaining 12% (CI: 2%-31%) improved from a stage 3 to a stage 2 following a levodopa challenge. The null hypothesis that the median of differences between the pre and post challenge H&Y stage equalled zero was retained using the Wilcoxon matched pairs signed rank test (p=0.083). The pre and post Levodopa challenge H&Y stage were highly correlated (Spearman's rho 0.85, p<0.01).

| | | **H&Y ON** | | | |
|---|---|---|---|---|---|
| | | **1** | **2** | **3** | **4** |
| **H&Y OFF** | **1** | 1 | 0 | 0 | 0 |
| | **2** | 0 | 9 | 0 | 0 |
| | **3** | 0 | 3 | 10 | 0 |
| | **4** | 0 | 0 | 0 | 2 |

**Table 6: Response to Levodopa in patients with postural deformity (H&Y)**

Twenty-two patients did not improve following a Levodopa challenge (as measured by H&Y grade), just three improved from a grade 3 to a grade 2.

## *Conclusion*

The postural measures following a levodopa challenge did not improve overall suggesting that postural deformities are not dopa-responsive phenomenon. When the subgroups were analysed separately there was negligible change to LF measures in any group, and only minimal improvement to the angle of TLF in those with camptocormia. Considering the axial akinetic rigid subtype predominance in these patients links can be drawn to a study which showed an absence of levodopa effect on axial tone in PD subjects (Wright et al, 2007). Wright and colleagues showed that increased rigidity about the trunk and hip in PD subjects (compared to controls) did not change following administration of Levodopa and the authors suggested this finding may underlie impairment of posture and mobility in PD patients. They concluded that their findings suggest that axial and limb tone are likely controlled by different neural pathways (Wright et al, 2007).

The postural responses actually deteriorated following supramaximal levodopa doses and this might reflect a side effect of excess levodopa – namely excessive sleepiness - which could limit any potential benefit, and was noted in a few patients post challenge. On the other hand it may reflect the patients' difficulty coping with the fine tuning (kinaesthesia or sensory awareness of body position and muscle activity) required to maintain postural control with more significant ON/OFF fluctuations. This kinaesthetic function has been found to be less effective when patients are using levodopa medication (Wright et al, 2010).

The limitation of this study is the small sample size within each subgroup and that fact that the postural measurements were taken only twice when 'off' and twice when 'on' ('usual' and 'best' attempt to stand up straight) and therefore does not reflect how postural measures change over longer periods of time. Challenge tests only monitor the immediate response to medication and not any potential benefits to posture that may occur later down the line, which the clinical vignette of a patient with significant camptocormia may suggest. The patient described was not aware of any benefits to posture following initiation or uptitration of levodopa or other dopaminergic

medication, and objectively he did not show any immediate improvement to levodopa or apomorphine challenges. However when his posture continued to deteriorate and in the absence of other treatment options, he was restarted on levodopa. After six months objective improvement in his Parkinson's severity and posture scores were noted. This suggests that, perhaps for posture, the effect of regular levodopa over a longer time frame may offer a more gradual effect than can be found on short-lived challenge response tests. In conclusion it appears that postural deformities in PD are not immediately dopa-responsive phenomenon like the other motor features such as tremor, rigidity and bradykinesia, but advocating levodopa aversion or removal following a negative levodopa challenge test is not recommended.

Our patients with postural deformity were slightly less responsive to levodopa (28% improvement in UPDRS motor score) compared to the level taken as a normal response (30% improvement) and supportive of a diagnosis of PD (Merello et al, 2002). Mean improvement in H&Y stage was just 0.12 following a levodopa challenge, a figure much lower than has been reported previously for PD (0.4 (Nova et al, 2004), 0.7 (O'Sullivan et al, 1998)).

In summary this study has shown that postural deformities of an average duration of 5 years appear mainly unresponsive to the immediate effects of a levodopa challenge and that supramaximal dosing of levodopa does not appear helpful for postural or other motor symptoms in this patient group. Patients should be made aware that dopaminergic medication is not a quick fix for an abnormal posture and there is a need to consider other non-pharmacological measures to combat these complications.

# Chapter 4: Radiological findings in Pisa syndrome and Camptocormia

## *Introduction*

The main aim of the research in this chapter was the detailed radiological evaluation of the postural abnormalities described in chapter 2 which demonstrated a range of sagittal, mixed and coronal plane deformities in patients with PD. An assessment of the flexibility of the deformities was made, scoliosis and other recognised orthopaedic conditions were sought and compared with non-PD adult deformity (e.g. degenerative scoliosis, kyphosis).

In this study the radiological findings in PD patients meeting criteria for Pisa syndrome are described. The question of whether Pisa syndrome reflects underlying scoliosis in PD patients is clarified, and if scoliosis is present, whether the skeletal abnormality is the same as that seen in adult de novo degenerative scoliosis. The proportion of the scoliosis that is attributed to collapse of posture is quantified and assessment is made of how 'fixed' the scoliotic deformity is in those with structural curves.

In the patients with camptocormia and moderate thoracolumbar flexion investigation of the main site of inflexion is made. The reducibility of the sagittal plane deformity in the recumbent position was also assessed and differences between PD patients with camptocormia and typical pure adult onset kyphosis are described. Correlation of 'persistent' sagittal malalignment (i.e. that measured on supine imaging) with the axial akinetic rigid subscore (a factor which may be indicative of severity of sagittal imbalance in camptocormia type deformity) was carried out.

## Pisa syndrome and scoliosis

In earlier studies, 'scoliosis' was often used to describe the clinical finding of lateral flexion in parkinsonian patients, without confirmation of a scoliotic curve on radiological imaging (Baik et al, 2009, Ashour and Jankovic, 2006, Grimes et al, 1987, Duvoisin and Marsden, 1975, Indo and Ando, 1980, Serratrice and Schiano, 1976). Scoliosis is defined as a curvature of the spine with a Cobb angle of $10^0$ or more in the coronal plane (as measured on a radiograph) combined with rotation of the vertebrae (Schwab et al, 2002). Scoliosis that presents for the first time in the adult typically occurs in the lumbar spine and develops as a result of asymmetrical spinal loading, disc degeneration and facet joint failure ('de novo' or degenerative scoliosis). In pure adult deformity there are often two lumbar curves present, a lower lumbar curve causing the patient to laterally deviate to one side and an upper lumbar or thoracolumbar curve compensating for the curve below in an attempt to align the head over the midpoint of the sacrum so that the spine is balanced in the coronal plane (Birknes et al, 2008, Berven and Lowe, 2007). If the compensatory curve fails to completely correct the lateral flexion and tilt of the lower lumbar curve, then the patient will be imbalanced and have coronal shift to the concavity of the lower curve (and the convexity of the upper curve) (Figure 11A).

Scoliosis in the standing position reflects not only bone, muscle and soft tissue alterations (fixed and reducible changes) leading to spinal curvature but also the impact from 'collapse of posture' or failure of postural tone against gravity. In the supine position the latter is eliminated and the factors resulting in spinal curvature include the fixed bony deformity (e.g. spondyloarthropathy) and the 'elastic' connective tissue elements (e.g. muscle spasm or shortening, contractures). The flexibility of scoliosis can be considered to be due to a combination of collapse (the defect in postural tone against gravity) and impaired reducibility (the elasticity element of the deformity that can be eliminated with corrective forces) (Duval-Beaupere et al, 1985).

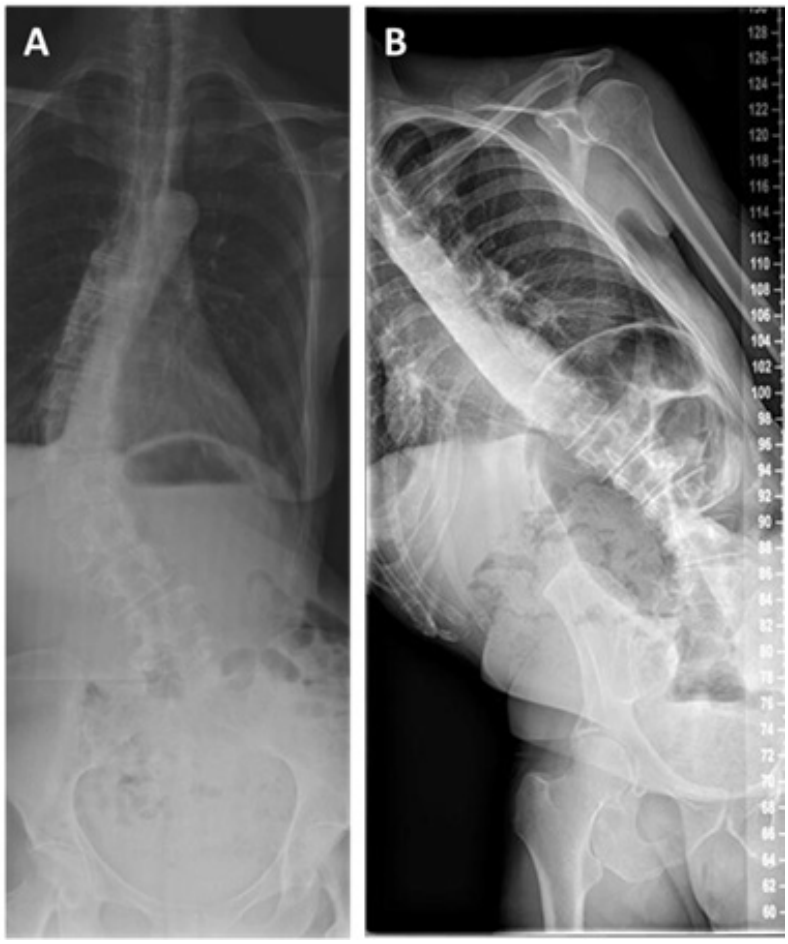



**Figure 11: Adult degenerative scoliosis versus Pisa syndrome associated scoliosis**

**A** Typical adult 'de novo' degenerative right-sided scoliosis (non-PD). Note the lower lumbar tilt convex to the left then and a right convex upper compensatory curve. The main (upper) curve is ipsilateral to the direction of lateral deviation of the trunk and has resulted in reasonable coronal balance as the head lies almost directly above the middle of the sacrum but the trunk remains shifted to the right.

**B** PD patient with severe Pisa syndrome and left-sided scoliosis. The convexity of the main curve is contralateral to the direction of lateral tilt (right) and there is no upper curve compensating for the coronal imbalance, giving the appearance of 'lumbar take-off'.

## Sagittal plane deformity

In the sagittal plane the composite of the lordotic and kyphotic regions of the spine should ultimately result in the head being aligned over the sacrum. When a plumb line is dropped from the centre of cervical vertebra 7 (C7) in the sagittal plane, it should fall within 2cm of the posterior superior corner of S1, this is known as neutral sagittal alignment or sagittal balance (Figure 12A). If a 2cm forward shift of this plumb line occurs then the patient is said to be malaligned or imbalanced in the sagittal plane. In normal aging there is a reduction in lumbar lordosis sometimes associated with an increase in thoracic kyphosis as a result of degenerative disc disease and less frequently vertebral compression fractures. To counterbalance this progressive kyphosis (and keep the plumb line in line with the posterior superior corner of S1) patients retrovert their pelvis (thereby increasing their pelvic tilt and flattening their sacral slope) (Lafage et al, 2008). When successful these patients are described as having 'compensated sagittal malalignment'. If the kyphosis progresses further additional compensatory mechanisms including knee flexion and hyperextension of the thoracic spine occur. If all the available compensatory mechanisms are employed to full effect and fail to align C7 over the sacrum then the' tipping point' is reached and the spine is described as being in 'decompensated sagittal malalignment' (Figure 12B).

A number of different spinal malalignments can be involved in the forward incline in Parkinson's patients – disproportionate antecollis at the cervical level, excess thoracic kyphosis due to stooping, rounding of shoulders or osteoporotic collapse, or a significant thoracolumbar flexion (camptocormia).

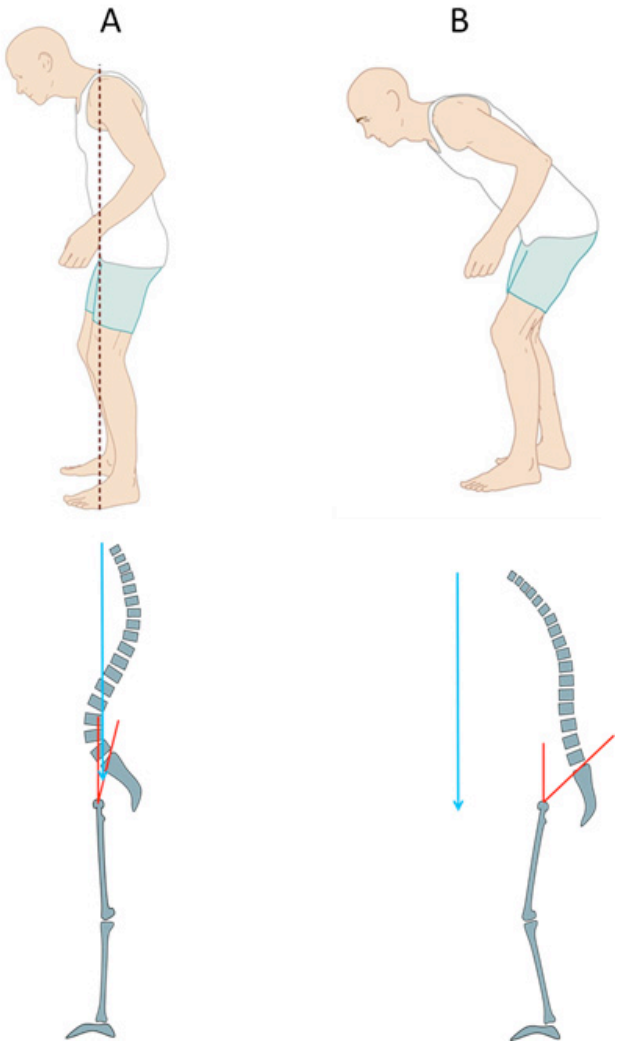



**Figure 12: Neutral and decompensated sagittal alignment**

**A** Normal sagittal spinal alignment and **B** decompensated sagittal malalignment. The blue arrow represents the C7 plumb line, the red lines represent the angle of pelvic tilt. In the kyphotic aging spine loss of lumbar lordosis is associated with the trunk pitching forward. Knee flexion, pelvic retroversion and hyperextension of the cervical and thoracic spine may then be employed in order to stand erect and maintain horizontal gaze. In this figure of camptocormia (B) the compensations are insufficient and the patient exhibits decompensated sagittal malalignment – the C7 plumb line shifting anteriorly to the sacrum.

*METHODS*

## Patient selection

Patients with PD and a clinically defined postural abnormality such as camptocormia, Pisa syndrome or other deformity based on the pre-specified criteria were included. Exclusion criteria for this aspect of the study included any females who were or thought they may be pregnant or any patient unable to stand unaided for the X-ray or lie flat for the CT scan (n=0). Patients were given time to consider participation after being provided full details of the study protocol and radiation exposure from the x-rays and CT scan. All patients described in chapter 2 took part in this study.

In order to understand the spinal changes underlying recognised clinical deformity syndromes, analysis was carried out in those with lateral flexion deformity and in those with sagittal plane deformity - camptocormia and moderate thoracolumbar flexion.

Fifteen PD patients met the clinical criteria for Pisa syndrome (subgroups C, D & E), 2 with compensated spinal curvature (subgroup F) and 9 with sagittal plane deformity only (subgroups A&B). The mixed group were analysed both for their coronal plane deformity (i.e. scoliosis) and also with regard to their sagittal plane deformity. In the Pisa syndrome group there were 12 males and 3 females with a mean age of 72 years and disease duration of 15 years. The Pisa syndrome had been present for a mean of 6 years (SD = 3) when studied although some patients gave as little as a few months history of deformity and some as much as 13.2 years. In the sagittal plane deformity only group there were 3 females and 6 males, the mean age was 72 years and mean disease duration 13 years, deformity had been present for an average of 5 years.

## Radiography methods

Plain X-ray and computerised tomography (CT) of the spine was carried out in all patients. Digital radiography of the whole spine ('scoliosis protocol') in the unsupported patient was performed using Philips Digital Diagnost version 2 (2.0.2.SPI). Coverage began at the external auditory meatus (EAM) and extended caudally to include the femoral heads. Patients were positioned by one researcher and one radiographer and were instructed with the following commands: 'We want to see what your spine looks like normally, so please stand as is normal for you the majority of the time'. Whole spine acquisition was acquired in two segments and stitched in a semi-automated fashion (the two films were automatically overlaid with final adjustments performed manually) to produce a whole spine radiograph (Figure 13A). Both Anterior-Posterior (AP) and lateral views were obtained. If it appeared that the entire spine would not be captured within the two windows (upper and lower) of the radiograph due to significant sagittal (lateral view) or coronal (AP view) imbalance then the priority was on gaining imaging of the lower spinal segments.

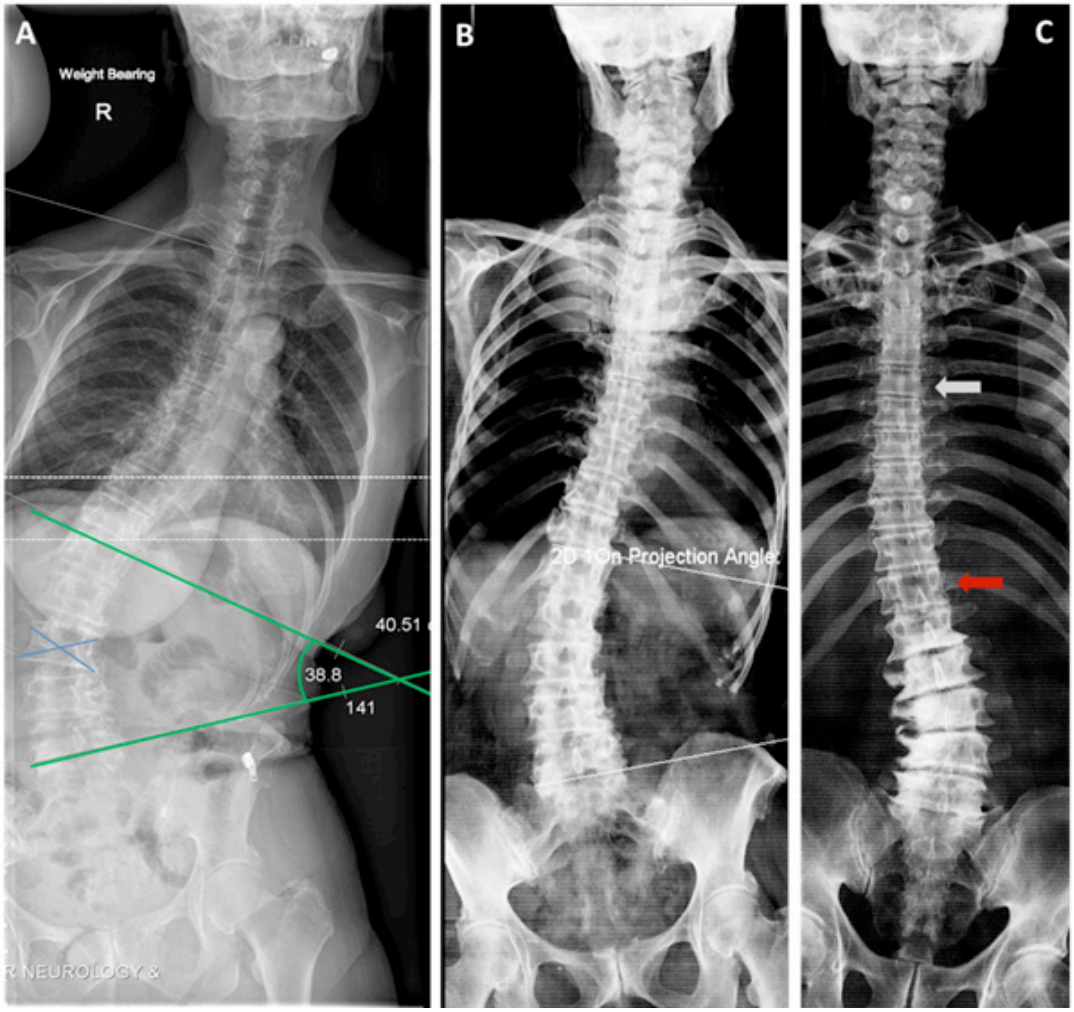



**Figure 13: Coronal plane measurements**

**A** Whole spine Anterior-posterior radiograph (patient standing). The area where the 2 images were stitched can be seen by the broken white lines. The apical vertebra of the primary scoliotic curve is crossed by 2 blue lines (centroid method). The cranial and caudal vertebra of the curve were selected and the Cobb angle of the curve measured as $38.8^0$ (green lines). **B** Two-dimensional radiographic projection reconstructed from the CT scan of the same patient in A, but in the supine position **C** Nash-Moe method for assessment of vertebral rotation: white arrow = grade 0 (neutral), red arrow = grade 1 (pedicles have rotated so that one is at the edge of the vertebral body).

CT scans were performed on a Siemens SOMATOM Definition AS 128 slice multidetector CT (Siemens, Erlangen, Germany). Patients were positioned by one researcher and one radiographer supine on the table with just one head support (identical for each patient), no additional cushions or supports were used in order to achieve a neutral unsupported supine position. The 'arms down' position (arms by the patient's side) was used in order view normal supine spinal alignment. Spiral acquisition of images with coverage from the EAM down to and including the femoral heads was performed. Acquired images were reconstructed on 0.6mm bone and soft-tissue algorithms which included a reconstruction of the true AP and lateral radiographic projection (to give a two dimensional (2D) maximal intensity projection composite) and a three-dimensional (3D) surface rendered reconstruction.

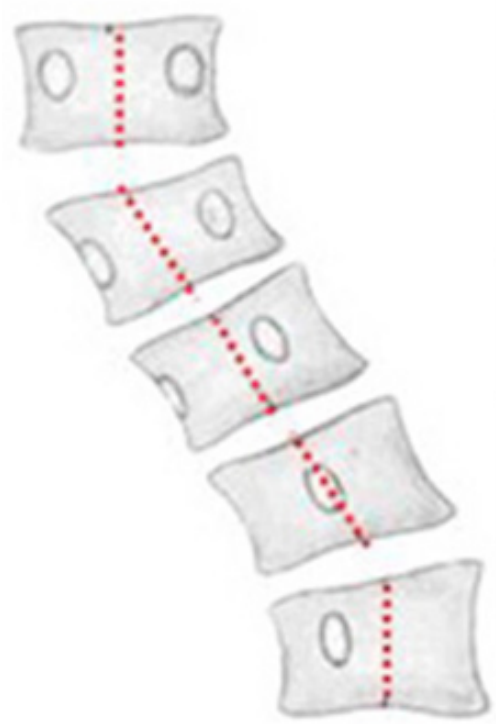
## Methods of analysis

The true AP and lateral radiographic projections reconstructed from the CT acquired data (Figure 13B) provided a dataset for like for like comparison with the standing radiographs (Figure 13A). Measurements of the spinal parameters were undertaken by 2 of the researchers on the radiographs and CT projections, measurements were taken based on the guidelines set out by the Spinal deformity study group consensus (O'Brien et al, 2004).

### Coronal plane measurements

The major curve was identified and assessed using the Cobb method (Cobb, 1948), this involved identification of the apical vertebra (i.e. the most laterally displaced, most internally rotated, but least tilted segment) followed by identification of the cranial and caudal end vertebrae from which the angle was measured (Figure 13A). The cranial and caudal end vertebrae selected to measure the scoliosis angle in the standing radiograph were also used in the supine CT derived images. The Nash-Moe method of assessing degree of vertebral rotation was graded for the apical vertebra (Nash and Moe, 1969) (Figures 14 & 13C). Scoliosis was defined as spinal curvature of at least $10^0$ measured by the Cobb method plus the presence of at least grade one vertebral rotation as

measured by the Nash-Moe scale. The relative collapse of scoliotic curves was calculated as the difference between the Cobb angle standing and supine divided by the Cobb angle standing as previously described (Duval-Beaupere et al, 1985). The 3D surface rendered images were used to assess osteophytic changes extending from the surface of the vertebrae. The number of vertebral bodies rendered fixed by osteophytic bridging was quantified.



| | |
|---|---|
| Grade 0<br>Neutral | Pedicles are symmetric |
| Grade 1 | Pedicle is at the edge of the vertebral body |
| Grade 2 | Pedicle is disappearing |
| Grade 3 | Remaining pedicle is in midline |
| Grade 4 | Remaining pedicle is beyond the midline |

**Figure 14: Nash-Moe scale for vertebral rotation**

## Sagittal plane measurements

The standing radiographs were examined for sagittal spinal alignment and location of flexion. Sagittal malalignment was described as regional if only a few vertebrae were causative of the significant anterior flexion and global if many vertebrae were involved (Scoliosis Research Society, 2013). The change to spinal curves from standing to supine was observed. Any significant antero or retrolisthesis (sagittal subluxations of one vertebra on another) and the grade of spondylolisthesis of L5 on S1 (Meyerding classification (Meyerding, 1931)) was recorded. The number and site of any vertebral fractures were noted if they resulted in significant loss of disc height and the osteophytosis between adjacent vertebrae quantified.

Sagittal alignment was measured as the distance between the C7 plumb line (C7PL) and the posterior superior corner of S1 (Figure 15B), this proved impossible on many standing radiographs as the patients cervical spine often extended beyond the edge of the radiograph window, but it was measured in all cases on the supine CT images. Sagittal malalignment was denoted by a deviation of the C7PL >2cm anterior to the posterior superior corner of S1(Malfair et al, 2010). In the standing radiographs and the supine CT derived sagittal plane images the following parameters were calculated using the Cobb method (Figure 15A):-

- Cervical lordosis: between the Atlas plane (a line intersecting the anterior and posterior tubercles of C1) and the caudal endplate of C7
- Thoracic kyphosis (between the upper endplate T2 and the caudal endplate of T12)
- Lumbar lordosis (between the upper endplate of L1 and the upper endplate of S1)

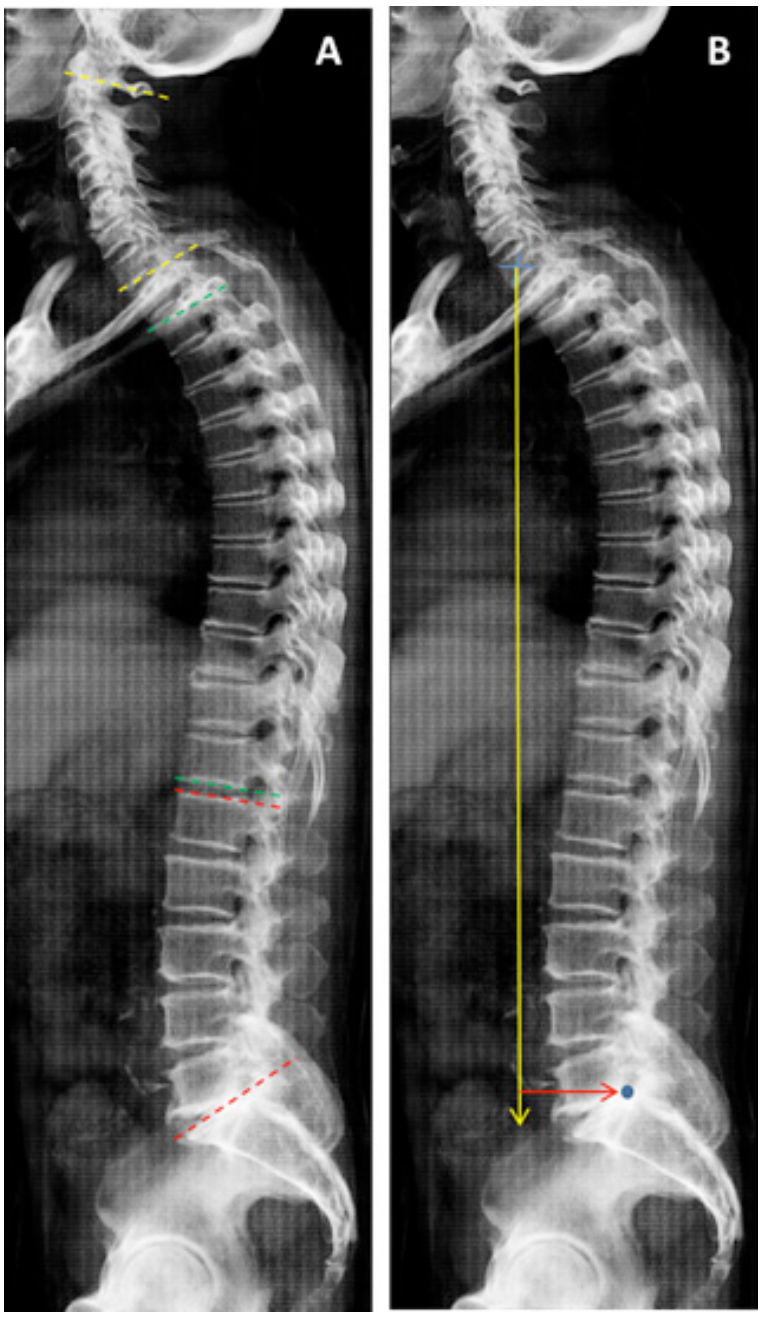



**Figure 15: Sagittal plane measurements**

**A** Measurement of cervical lordosis, thoracic kyphosis and lumbar lordosis using the Cobb method. Cervical lordosis was measured as the angle between the Atlas plane and the caudal endplate of C7 (yellow dashed lines), thoracic kyphosis the angle between the upper endplate of T2 and the caudal endplate of T12 (green dashed lines), and lumbar lordosis the angle between the upper endplate of L1 and the upper endplate of the sacrum (red dashed lines).
**B** Measurement of sagittal alignment. A C7 plumb line (C7PL, yellow arrow) was dropped from the centre of C7. The distance between the C7PL and the posterior superior corner of S1 (blue dot) gives the sagittal alignment (red arrow). (Measurements demonstrated on 2D radiographic projections from CT derived data).

The recognised parameter of pelvic incidence (PI) is unique to each individual, does not vary with position and governs the spinopelvic alignment. It approximates the lumbar lordosis (+/- $10^0$) in a sagittally aligned spine and so is utilised as a marker of the ideal lumbar lordosis for each participant. The PI is the angle subtended by a line drawn from the middle of the femoral heads to the midpoint of the sacral endplate and a line perpendicular to the sacral endplate (Figure 16). It is equal to the sum of the angles of sacral slope and pelvic tilt. It dictates the ability of the pelvis to retrovert and compensate for sagittal malalignment (Legaye et al, 1998). The pelvic incidence was measured on the CT derived data alone, the pelvic tilt and sacral slope were both measured on the standing radiographs and supine CT derived images (Figure 16). When the femoral heads were not perfectly aligned in the sagittal plane, a line connecting their centres was drawn and its midpoint joined to the sacral endplate midpoint for assessment of PI and PT.

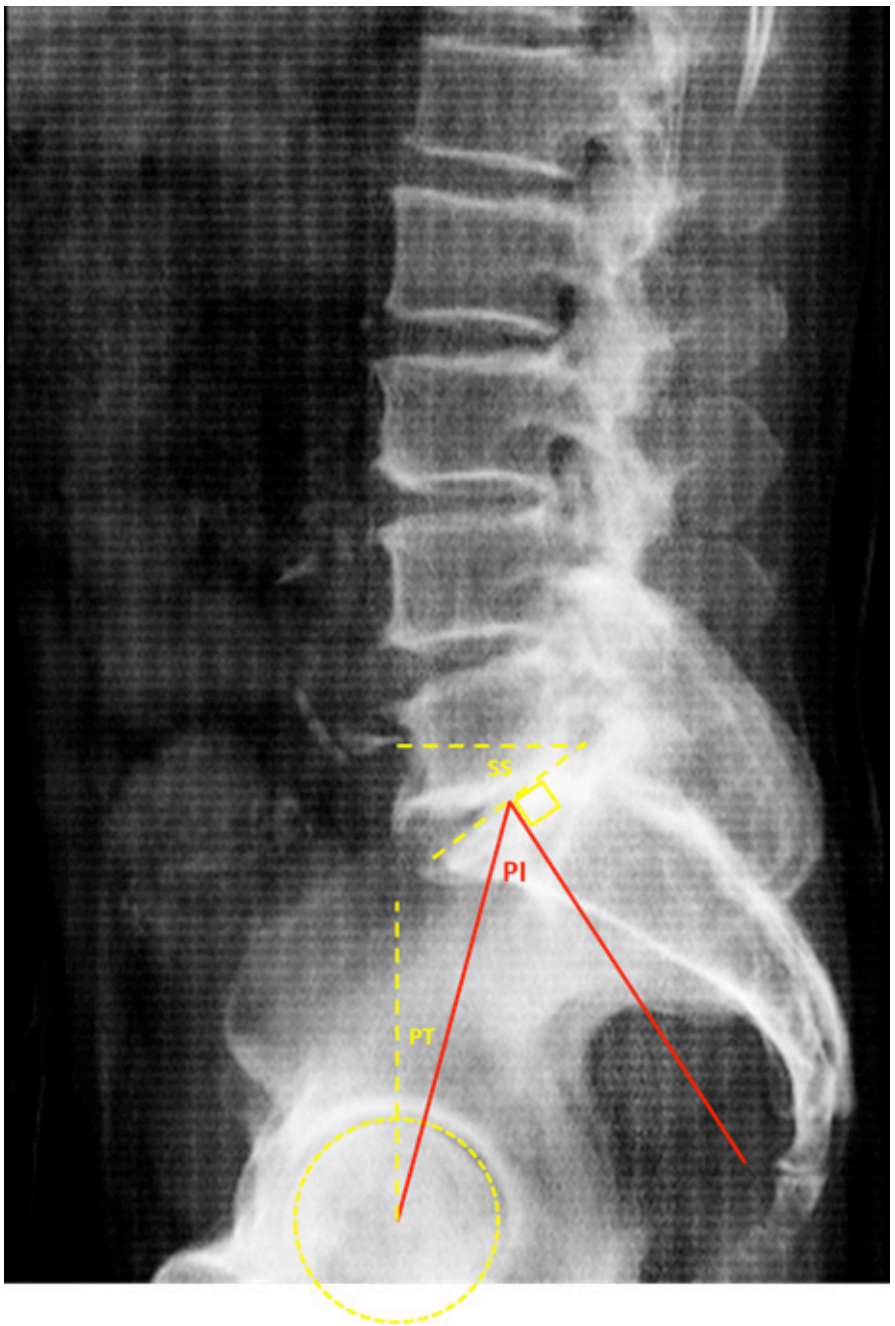



**Figure 16: Spinopelvic measurements**

Pelvic incidence (PI) is the angle subtended by a line drawn from the middle of the femoral heads to the midpoint of the sacral endplate and a line perpendicular to the sacral endplate. The pelvic tilt (PT) is the angle between the line drawn from the middle of the femoral heads to the midpoint of the sacral endplate and the true vertical. The sacral slope (SS) is the angle between the sacral endplate and the horizontal.

Analysis of the spinal parameters (radiographs and radiographic projections from the CT reconstructions) were performed on Agfa IMPAX picture archiving and communications systems (PACS) (IMPAX 6.4.0.4551, Agfa Healthcare N.V. Belgium, 2010) and viewed on 3 megapixel monochrome Barco monitors (Barco MXRT 5200). Analysis of the 3D surface rendered images was performed on Siemens Leonardo Syngo MMWP VE36A workstations (Siemens AG, Munich 2009). All radiographic devices utilised for acquisition, analysis and viewing were medical standard.

## Statistical methods

Radiological parameters were assessed for inter-observer correlation using Kendall's coefficient of concordance. All parameters used in the final analyses were deemed concordant at the significant level of $p=0.05$ and the mean of the concordant values used for further calculations. Clinical, demographic and radiological features from various subgroups (e.g. those with scoliosis on standing only and those with scoliosis on standing and supine imaging) were compared using student's t-test (95% confidence intervals) for continuous variables, Mann Whitney U test if data was skewed and Fisher's exact tests for nominal variables. Correlations were assessed by scatter plot and Pearson's or Spearman's rho tests and linear regression used to quantify associations. SPSS 19.0 statistical package was employed for all analyses.

*RESULTS*

The study group of 26 patients included 19 males and 7 females; there were no statistically significant differences when the mean of each spinal parameter was compared by the grouping of gender.

## Pisa syndrome

All patients with clinically defined Pisa syndrome had a radiologically defined scoliosis, of these 12 had a curve that persisted in the supine position (termed ‘structural scoliosis’) (Table 7).

| | Pisa syndrome patients | Mobile Scoliosis | Structural scoliosis | P value |
|---|---|---|---|---|
| Patients | 15 | 3 | 12 | |
| Age (years) | 72.1 (5.7, 63.3-82.3) | 70.5 | 72.5 | 0.6 |
| Male: Female | 12:3 | 2:1 | 10:2 | 0.5 |
| PD duration (years) | 15 (6.1, 7.3-27.3) | 15 | 15 | 0.99 |
| Deformity duration (years) | 5.8 (3, 0.6-13.2) | 5.2 | 5.9 | 0.7 |
| Daily Levodopa LED (mg) | 647 (242, 300-1197) | 666 | 642 | 0.9 |
| Daily Dopamine agonist LED (mg) | 250 (161, 0-480) | 275 | 244 | 0.8 |
| Daily PD medication LED (mg) | 1010 (330, 498-1697) | 1041 | 1003 | 0.9 |
| | | | | |
| Lateral flexion angle ($^0$) | 17.2 (5, 10-25) | 18 | 17 | 0.6 |
| | | | | |
| Standing x-ray Cobb angle ($^0$) | 35 (16.4, 8.6-67) | 20.8 | 38.8 | 0.08 |
| Supine CT Cobb angle ($^0$) | 20.4 (12.4, 3.2-45) | 6 | 24.8 | <0.01* |
| Relative collapse scoliosis (%) | 44.4 (21.4, 7.8-87.6) | 68.7 | 37.7 | 0.02* |
| | | | | |
| PDQ-39 total score (0-156) | 67 (26, 20-116) | 61 | 68 | 0.7 |
| WHO well-being index (0-25) | 13 (6, 3-25) | 15 | 13 | 0.6 |
| Fatigue severity scale (0-63) | 40 (15, 21-63) | 42 | 40 | 0.9 |
| Pain visual analogue scale (0-10) | 4 (2, 0-8) | 3.7 | 4.1 | 0.8 |
| | | | | |
| MOCA (0-30) | 22.6 (4.6, 10-27) | 21 | 25 | 0.4 |
| FAB (0-18) | 12.5 (3.8, 6-18) | 11 | 13 | 0.4 |
| | | | | |
| MDS-UPDRS II | 26 (5.6, 20-38) | 29 | 25 | 0.3 |
| MDS-UPDRS III | 43.5 (11.2, 27-61) | 50 | 41 | 0.2 |

**Table 7: Clinical and radiological parameters in those with Pisa syndrome**

No significant differences were found between those with and without a structural scoliosis in terms of Parkinson's disease duration, deformity duration, medication use, quality of life, pain, cognition or Parkinson's severity (UPDRS II & III). Values given = mean (SD, range). Key: PS Pisa syndrome; LED Levodopa equivalent dose; *significant difference between groups (Students t-test, Fisher's Exact test for gender); FAB Frontal assessment battery.

The mean percentage of scoliosis attributed to collapse of posture on standing was 44%;

this was significantly greater in the patients with mobile scoliosis (69%) versus those with a structural scoliosis (38%) (p=0.02, student's t-test). The group with 'structural scoliosis' had a slightly longer duration of deformity (5.9 versus 5.2 years), but this difference was not statistically significant (p=0.7, student's t-test). The mean patient age, PD duration and PD medication use did not differ between those with and without structural curves. Severity of posture as scored by the MDS-UPDRS III item 13 was scored as moderate in 3 patients and severe in 12, and the mean angle of lateral flexion was measured at $17^0$ from the vertical.

Similar to adult degenerative scoliosis, all patients had a very low apex to their scoliotic curve (L3 or L4 were most common) with evidence of lumbar degenerative changes. In terms of the compensatory response to the lumbar degenerative changes two particular phenotypes emerged. An atypical 'lumbar take-off' picture (a significant scoliotic curve located in the lower lumbar spine for which no correction to the midline was present) was most commonly seen (Figure 11B). In these 11 patients the convexity of the scoliosis was contralateral to the direction of tilt. The 4 remaining patients were more reminiscent of typical adult degenerative scoliosis with compensatory thoracolumbar curves attempting to correct for the lower lumbar curve and maintain coronal balance.

In 2 of the 3 patients with scoliosis on standing radiograph which resolved on supine positioning (Figure 17, top row) there appeared to be an attempt to stabilize the spine with osteophytic bridging between vertebral segments, but there was often also evidence of failed fusion or a cleft through the osteophytes which may explain why the scoliosis resolved in the supine position. This pattern of osteophytosis was also present in the majority of the patients with structural curves, but fused vertebral segments corresponding to the direction of lateral deviation rendering the deformity fixed was visible in only 3 of these 12 'structural curve' patients (Figure 17, bottom row). There was no association between the degree of lateral flexion (severity of Pisa syndrome) and Cobb angle of the underlying curve on the standing radiographs (Pearson's correlation 0.3, p=0.28) or supine CT scans (Pearson's correlation 0.1, p=0.62).

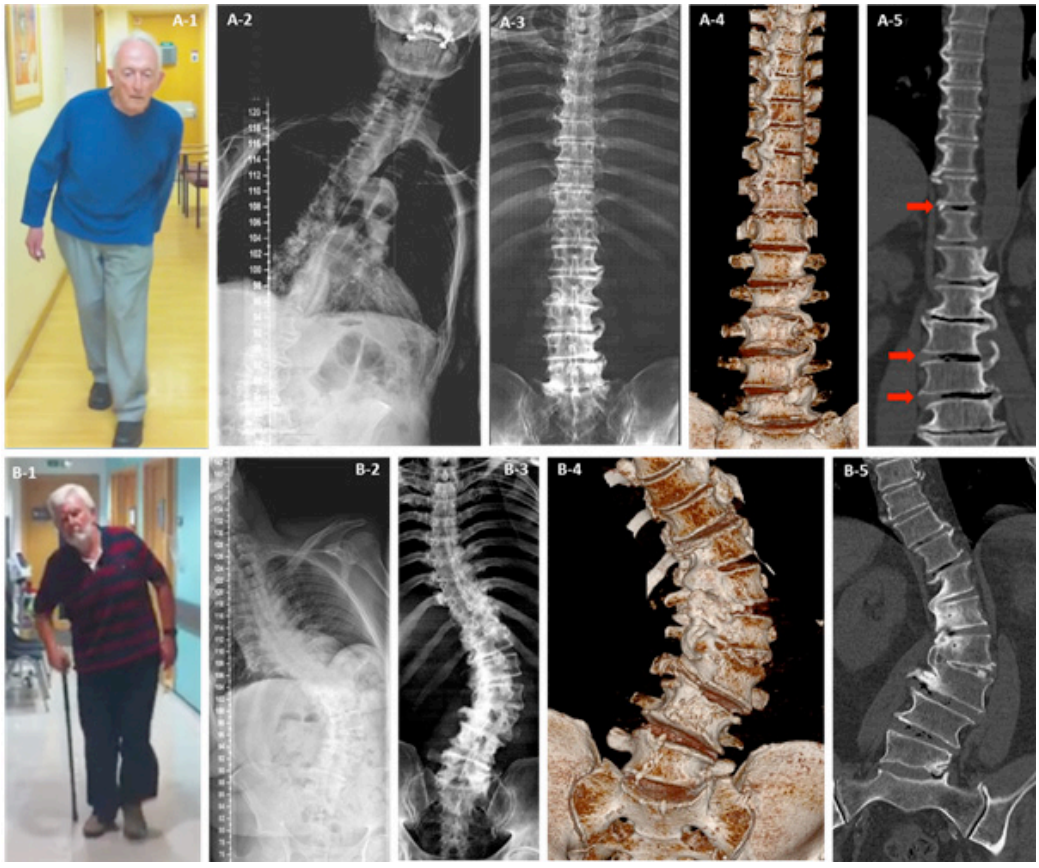



**Figure 17: Mobile and fixed skeletal changes in Pisa syndrome**

**Patient A** had scoliosis on standing radiograph (A-2) but not when he was scanned supine (A-3, A-4, A-5). There was evidence of osteophytic overgrowth below the apex of the scoliosis in the lumbar spine and above on the opposite side in the thoracic spine (A-4, A-5), this pattern suggests the degenerative changes were working to stabilise his spine but stopped short at the apex of his curve leaving him mobile but tilted at that level when standing (A-1, A-2). The reduction in curve with position, presence of interdiscal gas (red arrows on A-5) and gaps between the osteophytes are evidence that despite attempts the deformity is not fixed. **Patient B** had only minor improvement of his scoliosis on supine positioning (9% reducibility) (B-2, B-3). Fusion of vertebral segments due to complete osteophytic bridging at the apex of the curve was clearly seen (B-4, B-5) resulting in a fixed and possibly stable spinal deformity.

Key: 1 = Patient photographs of Pisa syndrome while walking; 2 = standing full spine AP radiograph; 3 = supine CT scan 2-dimensional composite image; 4 = supine CT scan 3-dimensional surface rendered image; 5 = supine CT scan 2-dimensional fine cut in coronal plane.

## Compensated spinal curvature

Both patients in this group had scoliosis as had been suspected from clinical examination and the curve patterns were typical of adult-onset degenerative scoliosis with large upper curves compensating for the inferior lumbar deviation. One patient with $0^0$ of lateral flexion (and $14^0$ thoracolumbar flexion) but clear pelvic tilting and asymmetry of knee flexion (Figure 18A-C) had a large curve with a Cobb angle of $65^0$ (Figure 18D). Relative collapse of her primary curve on supine positioning was just 28.6% (Figure 18E). Diminished lumbar lordosis ($12.7^0$) with partial (presumed osteoporotic) collapse of the L4 vertebra was also noted (Figure 18E).

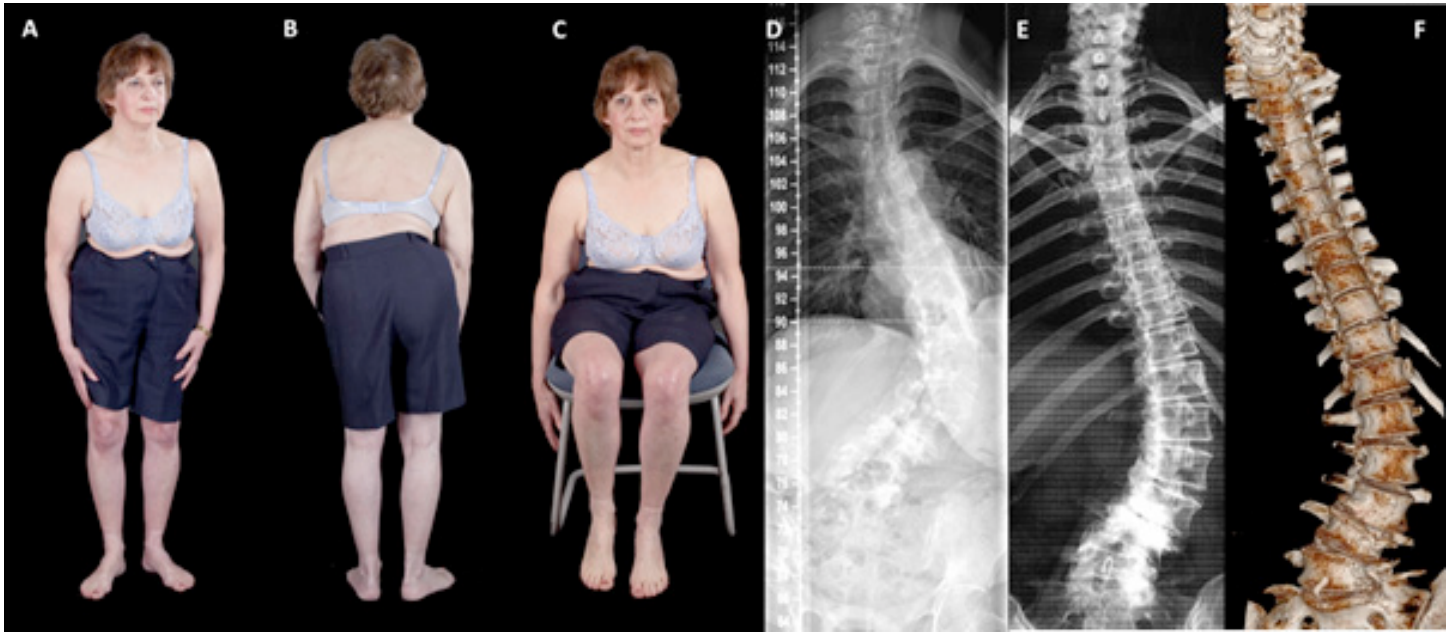



**Figure 18: Compensated spinal curvature**

This patient did not have Pisa syndrome (A), but examination of her posture from behind (B) and while seated (C) showed evidence of coronal plane deformity: asymmetry of shoulder heights and knee flexion, and a lateral pelvic tilt. Her standing radiograph was remarkable for a large but compensated curve (D) which did not alter significantly on supine imaging (E & F). Evidence of partial wedge fracturing of the lower lumbar vertebrae was evident (F).

## Sagittal plane deformity

The most striking feature on radiological imaging of those with sagittal plane deformity was a loss of the lumbar lordosis. On examination of the standing radiographs all but one patient exhibited lumbar alordosis, six patients actually presented lumbar kyphosis. Whilst all patients were able to improve their lumbar lordosis to some extent when recumbent, the majority had persistently flat lumbar spines (Figure 19), just three patients exhibited a reasonably lordotic lumbar curve.

Only three patients had a clear localized site of flexion or 'regional sagittal malalignment' (on standing imaging) and in all the site was lumbar or thoracolumbar. The remainder had the appearance of 'global sagittal malalignment' with many vertebrae throughout the spinal column seeming to contribute to the anterior tilt when standing.

Only one patient had significant spondylolisthesis (anterior or posterior vertebral displacement) - a forward translation of L5 on the sacral endplate (Meyerding grade 2). Wedge or partial vertebral crush fractures were evident in 4 patients (all the female patients and one male) and located in the thoracolumbar junction. The three female patients with sagittal plane deformity all had more than one partially collapsed vertebrae: L1-3; T11-12; T7,11 & L1-3 (Figure 20), the male patient had a partial collapse of T12. Significant osteophytosis rendering two or more adjacent vertebrae fixed was present in just 2 patients and in both was most prominent in the upper thoracic spine sparing the thoracolumbar junction and lumbar spine.

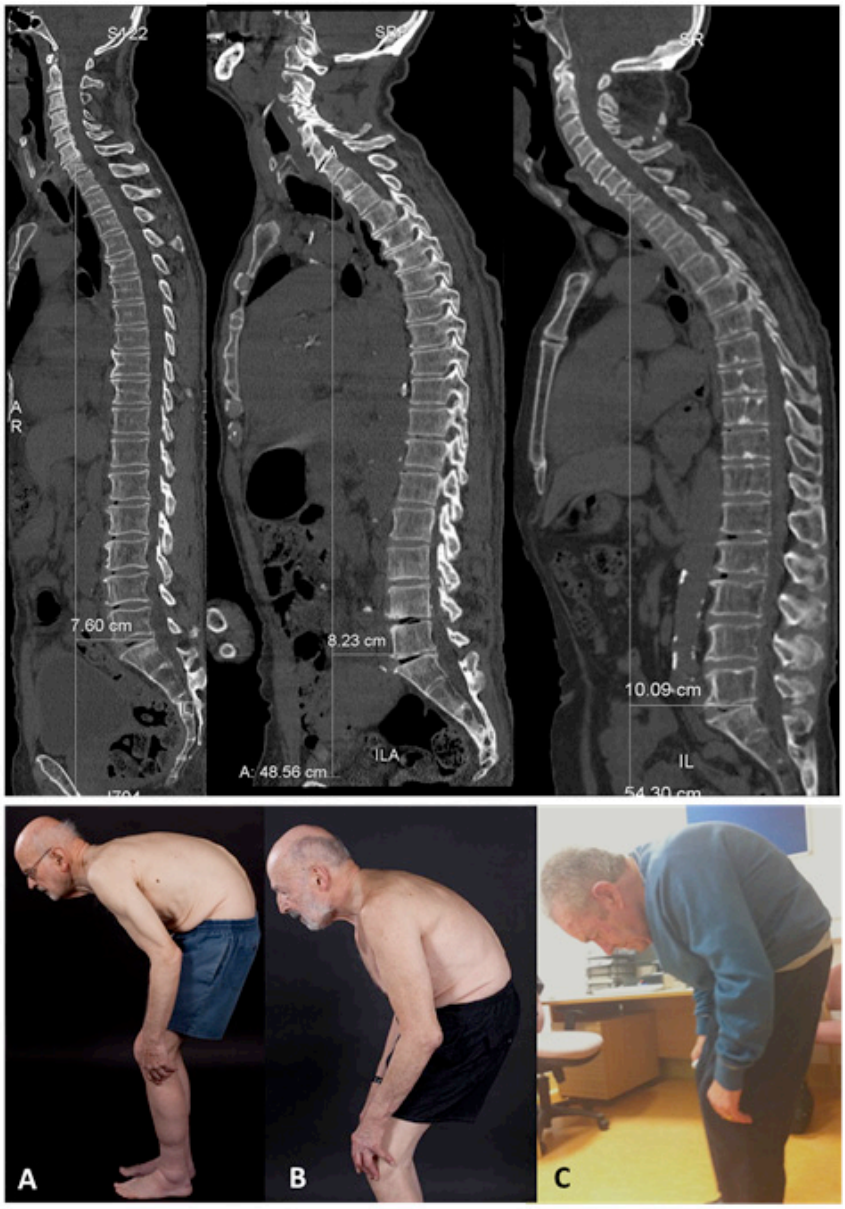



**Figure 19: Typical supine imaging findings in PD camptocormia**

Note the severe loss of lumbar lordosis (lumbar alordosis) or 'flatback' and the persistence of sagittal malalignment (>2cm). Patient A had a relatively straight spine throughout its length, patients B&C had more pronounced thoracic kyphoses. None of these patients had evidence of significant spondylolisthesis, osteophytosis or vertebral collapse contributing to their abnormal posture. Interdiscal gas can be seen in all three patients in the lumbar spine indicating instability or movement about this region (best viewed in B between L4/5 & L5/S1) (2D projection from supine CT imaging).

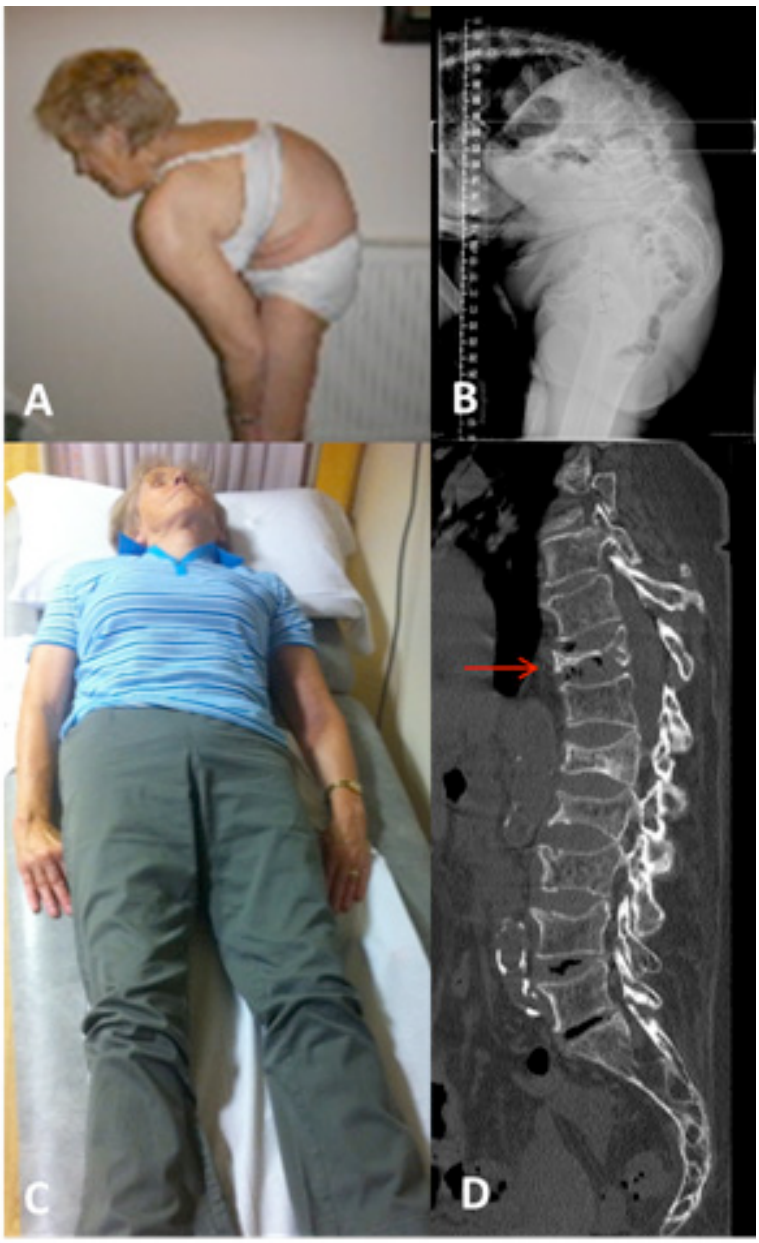



**Figure 20: Osteoporotic collapse in a PD patient with camptocormia**

This patient has a completely collapsed posture on standing (**A**&**B**) but when supine there is normal sagittal alignment of the spine and no flexed joint contractures (**C**). Supine CT imaging through the midline demonstrates several osteoporotic vertebral fractures (**D**). There is complete wedging of T11 (red arrow) and partial collapse of lumbar vertebrae 1-3 (**D**).

The mean pelvic incidence in the group was $56.5^0$, therefore the expected lumbar lordosis required for a sagittally balanced posture was $56.5^0$ (+/- $10^0$). In the standing radiographs the mean value of lumbar lordosis was $-0.8^0$ (i.e. $0.8^0$ of kyphosis), approximately 57 degrees (SD15, $-83^0$ to $-39^0$) out from that required for sagittal balance and even when supine there was an approximate mean deficit of $15^0$ (SD18, $-39^0$ to $11^0$) from that expected. In terms of pelvic retroversion the mean pelvic tilt when supine was $21.1^0$ (SD7, $11^0$-$30^0$) and on standing was $35^0$ (SD5, $26^0$-$42^0$) a mean increase of just 13.8 degrees, i.e. on average the pelvis retroverted by 13.8 degrees when patients stood (SD7, $3^0$-$22^0$) and accordingly the sacral slope flattened on standing. As a result all nine patients had decompensated sagittal malalignment when standing. This could not be quantified precisely as many of the patients were so imbalanced their cervical spine extended beyond the edge of the radiograph film. Only one patient was sagittally aligned in the supine position (Figure 20C). The remaining eight had improved but persistent sagittal malalignment (mean 6.8cm)(Figure 19). Cervical lordosis was only available to measure in a third of patients on the standing radiograph and thoracic kyphosis in 7 of the 9 cases. All measurements were made on all patients in the supine position. Mean values are given in table 8. Observation of the mean measurements shows there was no appreciable change to the magnitude of the cervical or thoracic curvatures on supine positioning, but the mean lumbar lordosis increased by $44^0$ when the patient lay flat.

| | Sagittal plane deformity only |
|---|---|
| Patients | 9 |
| Age (years) | 72.7 (4, 68-78) |
| Male: Female | 6:3 |
| PD duration (years) | 13.2 (5, 7-21) |
| Deformity duration (years) | 4.9 (3, 1-10) |
| Axial akinetic rigid subscore (0-28) | 11 (2, 7-15) |
| Thoracolumbar flexion angle ($^0$) | 48.3 (20, 27-90) |
| Lateral flexion angle ($^0$) | 3 (2, 0-7) |
| | |
| **Standing radiograph measures:-** | |
| Cervical lordosis ($^0$) | 48.5 (7,42-56)* |
| Thoracic kyphosis ($^0$) | 41.6 (15, 13-58)** |
| Lumbar lordosis (LL) ($^0$) | -0.82 (15, -26-22) |
| **Supine CT measures:-** | |
| Sagittal alignment (cm) | 6.8 (2.7, 1.5-10.5) |
| Cervical lordosis ($^0$) | 49.6 (13, 34-71) |
| Thoracic kyphosis ($^0$) | 40.8 (7, 29-49) |
| Lumbar lordosis ($^0$) | 41.5 (18, 23-74) |
| Pelvic incidence ($^0$) | 56.5 (9, 44-72) |
| Pelvic tilt ($^0$) | 21.1 (7, 11-30) |
| Sacral slope ($^0$) | 35.6 (11, 20-53) |
| Cobb angle of any scoliosis ($^0$) | 10.5 (12, 2-38) |
| | |
| Change to LL (supine - standing) ($^0$) | -44.1 (19, -74--14) |

**Table 8: Clinical and radiological parameters in sagittal plane deformity**

Measurement of cervical lordosis and thoracic kyphosis was limited on the standing radiographs as many patients extended beyond the edge of the radiograph (*based on 3 patients measurements, **based on 7 patients measurements). Note that the mean lumbar lordosis was negative indicating the measurement had become a kyphosis.

The sagittal plane parameters in the mixed group (i.e. those with sagittal and coronal plane deformity) showed a significantly worse mean lumbar lordosis compared to those with sagittal plane deformity alone. All seven patients in the mixed group had a kyphotic lumbar spine when standing with a mean lumbar kyphosis of $23^0$ versus $0.8^0$ in the sagittal plane deformity only group (Mann-Whitney U test, p=0.04). The remaining sagittal plane parameters did not differ significantly between the groups. Osteophytosis of adjoining vertebrae was detected in 4 of the 7 patients in this group but only involved 2 to 4 thoracic vertebrae in each of those, except for one patient. This patient was noted on clinical examination (Chapter 2) to have irreversibility of his anteriorly flexed posture when supine and although had never received a diagnosis of rheumatologic or orthopaedic condition he was found to have almost complete fusion of his spinal column resulting in fixed anterior flexion. He stated his abnormal posture first became apparent after his Parkinson's symptoms began but the radiological features are suggestive of co-incidental ankylosing spondylitis (Figure 21).

There was no significant spondylolisthesis or vertebral collapse fractures in any of the patients in the mixed group.

There was a strong linear relationship between 'persistent' sagittal malalignment (i.e. that measured supine) and axial akinetic rigidity subscore when those with secondary causes of sagittal malalignment were excluded (i.e. those with osteoporotic wedge fractures, severe spondylolisthesis and presumed ankylosing spondylitis) (both those with sagittal plane deformity alone and mixed deformity were included in this linear regression analysis). Persistent sagittal malalignment (mm) could be predicted from the axial akinetic rigid subscore by the following formula: persistent sagittal malalignment (mm) = 0.83 + 5.8 x Axial akinetic rigid subscore, $R^2 = 0.488$ (Pearson's correlation 0.7, p=0.017).

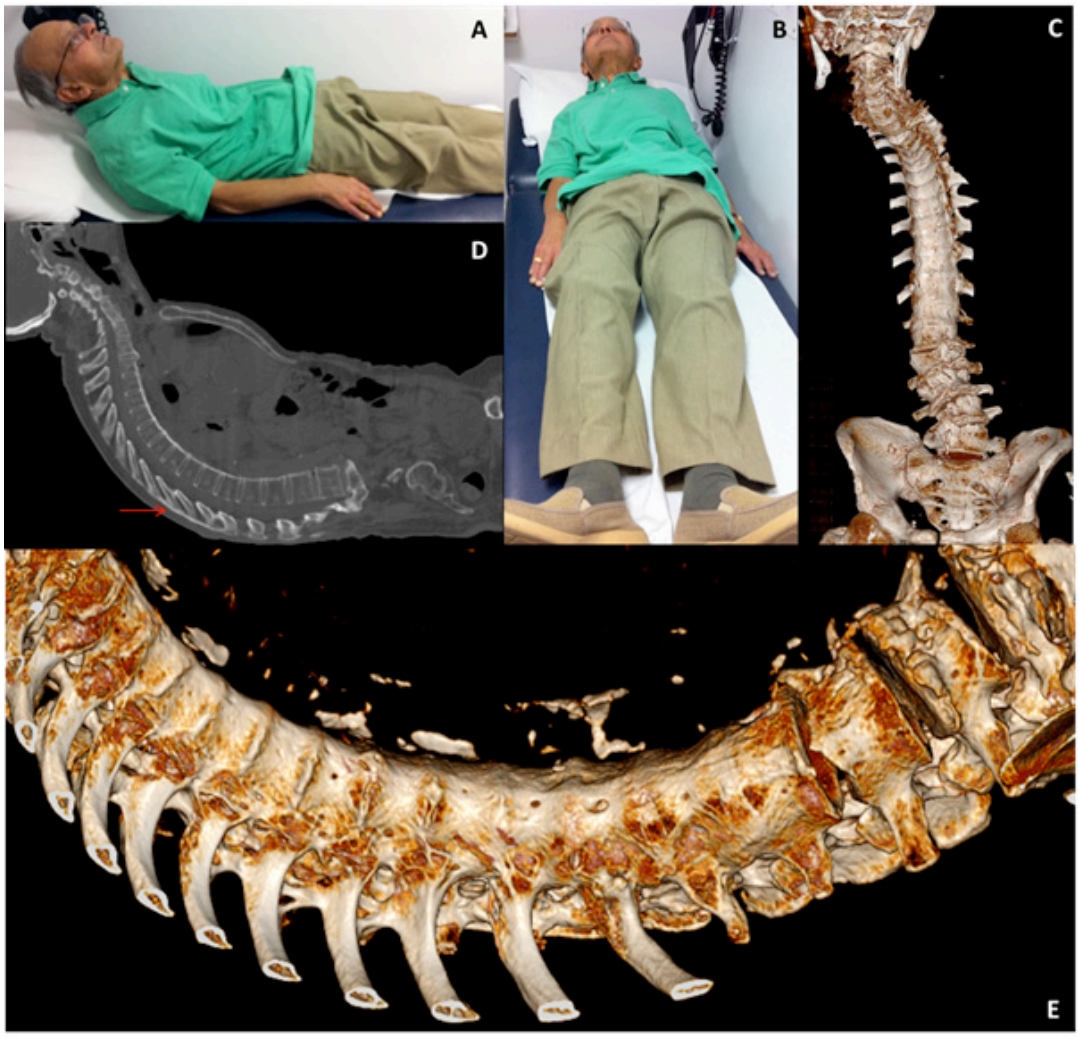



**Figure 21: PD patient with mixed deformity suggestive of ankylosing spondylitis**

The patient was unable to lie fully supine, his head remaining elevated from the pillow (A&B). Supine imaging revealed fusion of the C5 and C6 vertebral bodies and extensive syndesmophytes extending the entire length of the thoracic spine holding it in kyphosis (C-E). Calcification of the anterior spinous ligament (C-E) and supraspinous ligament (red arrow in D) was also evident. Severe degenerative disease of the lumbar spine was evident, with a scoliosis centred on L4/5 and loss of disc space (C&E).

Key: C&E = supine CT scan 3-dimensional surface rendered image; D = supine CT scan 2-dimensional fine cut in sagittal plane.

## Pisa syndrome and scoliosis

This study has provided evidence that scoliosis and Pisa syndrome are distinct entities. Although all patients with Pisa syndrome had radiologically confirmed scoliosis, this was not always structural, involved a large element of collapse and differed from that seen in adult degenerative scoliosis. It has also shown that scoliosis can be present in PD patients without Pisa syndrome and therefore non-spinal compensations rendering patients free from a defined postural deformity syndrome should not be overlooked.

The Pisa syndrome patients who listed to the right had a left sided scoliosis and vice versa, resembling a failure to stand upright in the coronal plane. Most exhibited a single C-shaped curve as has been previously described (Tassorelli et al, 2012). In contrast, patients with 'de novo' adult scoliosis often list to the side of the upper compensatory curve (which is normally the larger of the curves in adult degenerative scoliosis, S-shaped curve) (Figure 11).

This study has confirmed that a large element of the deformity in the Pisa syndrome patients is due to collapse and reflects their inability to produce erect posture in the presence of normal physiological loading of the spine (standing). The relative collapse of 44% found in the studied patients is a much greater figure than that reported in the literature in adult (30%) (Perennou et al, 1994) and adolescent (19-31%) (Zetterberg et al, 1983) scoliosis patients. Detailed CT reconstructed images showed that of the 12 patients with structural curves only 3 had evidence of complete fusion between vertebral segments at the site of their curves. In the majority there existed non-bony changes holding their spine curved even when they were supine probably due to increasing muscle rigidity and muscle shortening, secondary disuse atrophy, and connective tissue changes. The lack of stabilising rigid struts (osteophytic bridging between vertebrae) however, means that there is a risk that any lateral deviation could exacerbate over time.

Patients with long standing PD, medium-to-long term deformity and moderate to severe

posture were studied. In patients with subacute onset of mild Pisa syndrome, the deformity is likely to be more mobile and the radiological findings less pronounced. Although this study examined the differences between those with and those without structural scoliosis it may be that these are two points on a spectrum. Advancing age, disease duration, disease severity, medication use and cognition do not seem to influence the propensity to develop a more immobile (and potentially stable) curve. Although the mechanism may differ from other types of scoliosis this study raises an important question: does PD accelerate a degenerative process in those with a propensity to develop a curve, or is PD a risk factor for scoliosis? We favour the latter explanation because degenerative scoliosis is most likely due to asymmetrical loading of the spine and in PD this may be inferred from the asymmetry which is a common but not invariable feature of PD, and the loss of postural tone or righting reflexes when a patient does begin to list to one side.

## Sagittal plane deformity

In Parkinson's disease there is increased axial tone and restricted range of movement of the spine (Wright et al, 2007). Various studies have shown reduced (Schenkman et al, 2001, Franzén et al, 2009, Nikfekr et al, 2002) and delayed (Vaugoyeau et al, 2006) segmental excursions around the spinal axis. It is possible that these mechanisms in PD patients are similar to the consequence of long instrumented spinal fusion in adult deformity patients (La Grone, 1988), i.e. these patients are at risk of sagittal malalignment because of the structural inability to compensate. The strong correlation between higher axial akinetic rigidity sub-scores and sagittal malalignment supports the proposal that less effective spinal movement due to chronically abnormal axial tone is in part causative of lumbar lordosis flattening. While lumbar alordosis may reflect a particular spinal shape, which predisposes to camptocormia in those with PD, it is more likely to be the result of Parkinson's disease on the axial musculature (particularly in those with axial rigidity predominant disease). The resulting functional semi-rigid deformity in the PD deformity patients may then make them less able to compensate for both the normal aging process of anterior degenerative spinal disease but also the specific Parkinsonian 'propensity to bend the trunk forward' (Parkinson, 1817). The

striking lumbar alordosis when the patients were supine means they are already mechanically disadvantaged before they stand. On standing, pelvic retroversion and sacral slope flattening was marginal and insufficient to achieve sagittal alignment. The limiting factor likely being restriction to hip joint extension, earlier clinical examination was notable for the consistent finding of tight hip flexors and in some patients hip flexion contractures, a recognized limiting factor for pelvic retroversion (Roussouly and Pinheiro-Franco, 2011). If the sagittal plane deformity becomes chronic it may result in overactive hip flexors (psoas major, rectus femoris, iliacus) which in turn result in unwanted reciprocal inhibition of the gluteal muscles. These weak gluteals may result in further loss of the lumbar lordosis, because now the lumbar spine needs to 'lock' to provide support superiorly, i.e. the straightened and rigid lumbar spine forms a basis from which the patient has a base of support in the absence of good gluteal function and spinopelvic alignment. The difficulty in having a 'locked' lumbar spine means that there is likely to be rigidity of the spinal axis superiorly and as a result the global axial rigidity means that the shoulder and pelvic girdles can't function independently and the patient moves and turns 'en bloc' with subsequently less spinal excursions and less ability to fine tune to disturbances of balance.

This study has corroborated the clinical findings that camptocormia is not fully reversible when the patient is recumbent with sagittal malalignment persisting on supine imaging. It has also provided radiological evidence that the thoracolumbar spine is the major location to succumb to anterior spinal loading and as such is the apex of the flexion deformity in patients with camptocormia. Although a specific point of anterior flexion was not always easily identifiable on the standing radiographs, CT imaging provided proof of focal instability in the thoracolumbar region - vacuum phenomenon (interdiscal gas) in the thoracolumbar region suggestive of discs that are unable to withstand the required physiological demand of that segment and thus may collapse forward when the patient stands.

The greater deficit in lumbar lordosis measured in those with mixed deformity is explained by the three-dimensional quality of kyphoscoliosis malformations. A rotational deformity of the spine flattens the lumbar lordosis, thereby resulting in a

combined kyphoscoliotic posture.

The severity of sagittal malalignment seen commonly in PD related camptocormia is seen in adult deformity cases only rarely and usually in female patients. While most adult kyphotic deformity patients also have thoracolumbar disease, other sites of flexion deformity may be contributory (e.g. upper thoracic region in those with an osteoporotic Dowager's hump). Osteoporotic vertebral collapse was invariably found in the female patients in this study (but in the thoracolumbar region rather than the upper thoracic region) but significant spondylolisthesis was rare. The patients did not demonstrate thoracic hypokyphosis, perhaps this compensatory mechanism is precluded in PD by axial rigidity.

A limitation of this type of study is that radiological examination at one time point fails to evaluate the evolution of postural deformity, including the contribution of functional adaptions due to pain (i.e. antalgic posture) and the change to posture with fatigue. The study group was small and lacked a control group of non-PD adult deformity patients or PD patients without postural deformity for direct comparison. X-ray and CT are excellent imaging modalities for bony deformity but are not specific for investigating potential causes of postural deformity secondary to irritative phenomenon such as intrinsic cord malignancy and nerve root irritation (Goldstein and Waugh, 1973)

## *Conclusion*

Camptocormia and Pisa syndrome in Parkinson's disease are different to the sagittal plane deformity and degenerative scoliosis encountered in typical age-related adult onset deformity. Long-standing moderate-to-severe Pisa syndrome is often associated with underlying axial skeletal deformity, typically true rotational scoliosis, but a large proportion of the scoliosis reflects collapse or impaired postural tone. This study has provided evidence that camptocormia in Parkinson's disease is a state of decompensated sagittal malalignment. It may be that earlier in the course of the deformity or in patients with 'stooped PD', the spine may remain in compensated sagittal malalignment, i.e. the patient is balanced in the sagittal plane due to knee flexion and pelvic retroversion. Whereas the severity of camptocormia reflects extension beyond the point in which compensatory mechanisms function effectively. Once this 'tipping point' has been reached trunk muscles which previously functioned as extensors may only be able to function as flexors of the spine causing continued kyphosis. The radiological findings suggest that true camptocormia in PD is characterised by loss of the lumbar lordosis relative to the pelvic incidence and an absence of alternative spinal pathology (e.g. vertebral fracture, spondylolisthesis, ankylosing spondylitis). PD is a risk factor for kyphosis but the severity of sagittal plane deformity typical of camptocormia may be specific to those with axial predominant disease and a susceptible spinal shape. Radiological imaging is important for exclusion of concurrent conditions which may mimic Pisa syndrome or camptocormia, especially if there is clinical suspicion of osteoporosis or the postural abnormality predated the onset of Parkinson's symptoms.

# Chapter 5: Non-Parkinson's postural deformity in the movement disorder clinic

## *Introduction*

Camptocormia can present to neurologists, orthopaedic surgeons, rheumatologists and various other medical disciplines. The true aetiology can remain elusive in many patients and the specialization of the physician or surgeon may reflect the final diagnosis given. Jankovic's series of 16 patients with camptocormia presenting to a movement disorder clinic was made up of 11 patients with Parkinson's disease (PD), 2 with primary axial dystonia, 2 with secondary dystonia (due to disc surgery, syringomyelia) and 1 with Tourette syndrome (Azher and Jankovic, 2005). Laroche et al reviewed 63 patients presenting to a rheumatology clinic with camptocormia (Laroche and Cintas, 2010). Only 23 received a neurological diagnosis (including PD, limb girdle muscular dystrophy and myotonic dystrophy), whereas 40 received, as a diagnosis of exclusion, a label of delayed-onset paraspinal myopathy.

## *Aims and methodology*

Investigation of the variety of causes of camptocormia presenting to Neurologists with a special interest in Movement Disorders was undertaken. Review of all patients attending a tertiary movement disorder clinic who had received a diagnosis of camptocormia or bent spine syndrome and who did not have a firm diagnosis of Parkinson's disease over a 3 year period (August 2009-August 2012) was made. An additional patient with camptocormia and concomitant PD and muscular dystrophy (Patient four) is discussed.

All cases seen in one of the Movement Disorders clinic at Queen Square with bent or tilted spinal columns were re-examined paying specific attention to their musculoskeletal system.

*Results*

Six patients with camptocormia and three with Pisa syndrome/scoliosis were identified and are described below.

## Patient one

This patient presented at age 70 with an 11-year history of back pain, not helped by a lumbar laminectomy, but for one year had become increasingly bent the further she walked. Her elder sister, who suffered from Parkinson's disease, also had a flexed posture when she walked and had recently become wheelchair-bound. Their father had returned from the First World War with a bent spine.

She stood with neck and trunk leaning back and her arms extended behind her. She found walking upright uncomfortable and preferred to walk with her spine flexed to 90 degrees (Video 3). No weakness, pyramidal or parkinsonian signs were found on examination. A diagnosis of idiopathic axial dystonia with a possible *geste antagoniste* (extending her arms out behind her when walking upright) had been made by one neurologist, while another felt a paraspinal myopathy was more likely. Anticholinergic therapy and botulinum toxin injections were not helpful.

On follow-up five years later she still walked with severe camptocormia but had learned to walk erect by extending her arms behind her and locking her hands behind her back. On lying prone, she was unable to extend her trunk; she also had difficulty rising from a supine to seated position. She now had mild weakness of deltoid, supraspinatus and triceps muscles. There was no scapular winging and no facial weakness, but she did comment on a new difficulty in whistling. Beevor's sign (headward deviation of the umbilicus on neck flexion resulting from weakness of the lower rectus abdominis) (Beevor, 1904) was absent (Video 3). Investigations including creatine kinase (CK), immunoglobulins, thyroid profile and antibodies, acetylcholine receptor antibodies, spinal imaging and electrophysiological studies were all within normal limits. Given the mild shoulder girdle weakness and family history, her DNA was sent for analysis.

This revealed a gene rearrangement on chromosome 4q35 (Blnl resistant fragment measuring 34kb) confirming a diagnosis of facioscapulohumeral dystrophy (FSHD). Despite her normal electrophysiological studies an inherited myopathy was strongly suspected. It is likely this autosomal dominant muscular dystrophy was also the cause of her father and sisters abnormal posture.

## Patient two

The patient was of non-consanguineous Ashkenazi Jewish descent. She first presented to a neurologist at the age of 66 with a 9-year history of involuntary bending of her spine when walking. Any attempt to overcome the forward flexion led to shortness of breath and increased difficulty walking. Pushing a shopping trolley caused significant improvement in her posture. She also complained of a tight band sensation around her upper abdomen. She had a past history of rheumatic fever aged 8 years (no history of chorea) with subsequent mitral valve disease necessitating replacement with a prosthetic metal valve at the age of 46. Six years before presentation she had an episode of presumed polymyalgia rheumatica (based on symptoms of pain and stiffness around her neck, shoulders and upper arms and an elevated ESR – between 40-50mm/hr) which settled with a short course of steroids. She also had an 8-year history of deafness in the left ear. Her medications included warfarin, digoxin, bisoprolol, losartan, furosemide, spironolactone and quinine sulphate. She had never been exposed to dopamine blocking drugs. Her mother had a similar posture in her later years.

On examination she had spontaneous flexion of the trunk, which worsened the further she walked. Using a rollator or placing her hands on her thighs enabled her to straighten her trunk (Video 4). There was no fixed deformity when lying supine and spinal imaging revealed multi-level degenerative changes but no spinal cord compression or radiculopathy.

She was diagnosed with camptocormia due to idiopathic axial dystonia. DYT1 testing was negative. Focal myopathy was considered a possible cause but electromyography was felt to be contraindicated due to her treatment with warfarin. L-dopa (150mg/day) and anticholinergic drugs (trihexyphenidyl 6mg/day and tetrabenazine 12.5mg/day)

were ineffective but physiotherapy was of considerable benefit in improving her walking. At review 2 years later it was noted she had mild weakness of her hip extensors. She mentioned that her daughter was being investigated for ptosis. She admitted to never being good at sports and being unable to whistle. Examination revealed thinning of the muscles of the chest and neck (Figure 22) but no focal wasting or winging of the scapulae. She showed minimal weakness of the face (eye closure and puffing out her cheeks), some weakness of cough and sniff, and her vital capacity was reduced to 1.33 litres. She was able to lift her arms above her head when seated but not when standing. Trunk extension from the prone position was poor. Her CK was mildly elevated at 183IU/L (normal range 26-140). Late onset FSHD was suspected given the facial and limb girdle pattern of weakness, family history and similarities to the previous case. DNA restriction analysis revealed a fragment size of 34kb representative of a gene rearrangement on chromosome 4 specific to the diagnosis of FSHD. Her daughter also requested genetic testing and was also found to have inherited the fragment associated with FSHD.

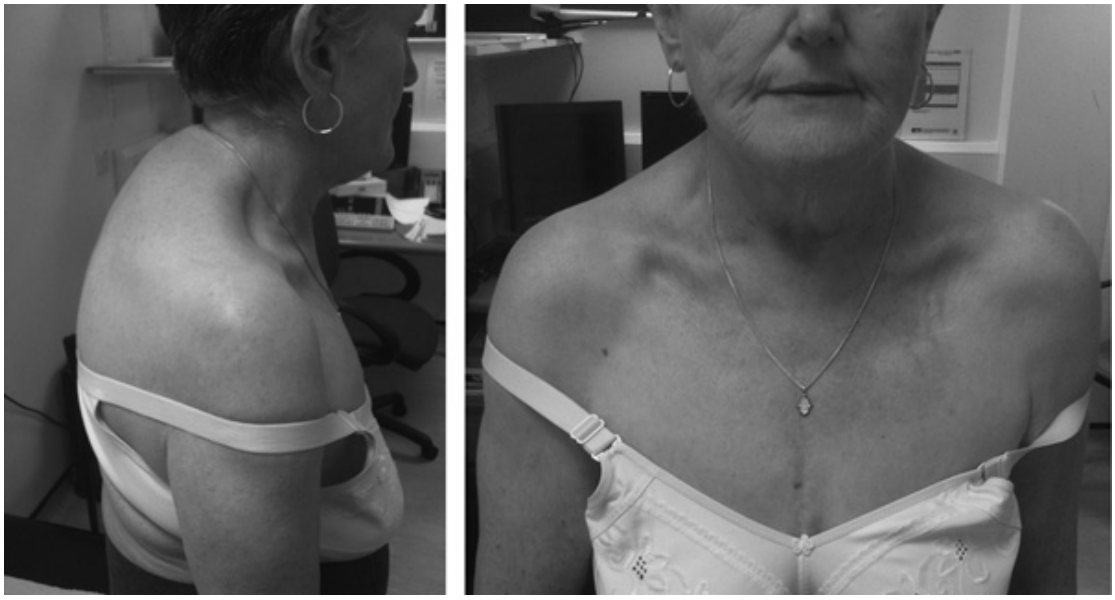


**Figure 22: The décolletage sign**

Note the thinning of the upper pectoral fibres over the clavicles.

## Patient three

A 63-year old female presented with a forward stooped posture when standing and walking and had started using walking poles for support. The problem had been getting slowly worse for the past 8 years and she had seen numerous specialists without conclusive diagnosis or successful intervention. She recalled her first problem being an inability to carry heavy objects unless she held them very close to her chest. She described her lower back feeling weak as if it was unable to support her. There was no family history of neurological illness. On examination she walked with $30^0$ thoracolumbar flexion with her hands resting on her thighs just above her knees, she had a slight valgus deformity of her knees. She was able to lie fully recumbent and there was no evidence of paraspinal muscle wasting. There was no evidence of sustained involuntary contraction of the anterior abdominal musculature. Spinal imaging revealed incidental cervical spondylosis and lumbar scoliosis. She was diagnosed with camptocormia of unknown cause and despite the absence of parkinsonian signs a trial of levodopa (Co-Beneldopa 125mg 4/day) was given and was ineffective. A second neurology opinion a few years later revealed a hint of head flexion weakness, very mild left hip flexion weakness and prominent weakness in the lower back when lying prone, a diagnosis of isolated paraspinal myopathy was felt possible and she was referred on to a neurologist with a special interest in neuromuscular disorders. At this review the patient was noted to have thinning of the periclavicular muscles, variable camptocormia when walking and the Gower's manoeuvre was observed when she was getting up from the floor (Video 5). Her CK was measured at 253IU/L, AChR antibody was negative and FSHD genetic analysis negative (Blnl resistant fragments both >48kb). EMG was not performed as she was taking warfarin for paroxysmal atrial fibrillation. While undergoing cervical spine decompression a paraspinal plus right deltoid muscle biopsy was performed and showed changes compatible with a mitochondrial myopathy (significant numbers of red ragged fibres, lobulated fibres with abnormal accumulation of mitochondria and SDH positive/COX negative fibres plus abnormal respiratory chain enzyme analysis), although mitochondrial DNA studies did not find a common mutation or deletion.

## Patient four

A 65-year old man with mild camptocormia and a diagnosis of Parkinson's disease presented with a positive genetic test for FSHD. He had presented 7 years earlier with catching of his left foot when he walked followed by left leg tremor, and following examination by a Neurologist and an abnormal DaTscan he was diagnosed with Parkinson's Disease. Flexion of his trunk had been present for 2 years prior to the diagnosis of PD which gradually deteriorated despite good response of most of his other symptoms to his PD medication. Eventually he began walking with a stick to limit the forward flexion. A family history of FSHD was brought to his attention and he also tested positive. Examination and investigation was performed to clarify if his camptocormia was due to his Parkinson's disease or his muscular dystrophy.

On examination there was clear shoulder girdle wasting and evidence of a décolletage sign. He had mild facial and neck flexion weakness and was completely unable to perform trunk extension from the prone position. When he stood he exhibited Gower's manoeuvre and he walked with significant camptocormia with his hands pressed on his thighs for support (Video 6). He had full reversibility of camptocormia when supine without hip or knee flexion contracture and when asked to stand against a wall showed good improvement to his posture although he had to use his hands to support himself. Electromyography of his facial, shoulder and back muscles showed evidence of myopathy (low amplitude very short duration motor unit potentials and fibrillation potentials) in his thoracic paraspinals and trapezius, he had difficulty recruiting the lumbar paraspinals. In the 'off' state (>12 hours since taking medication) his Parkinsonian signs were mild and he scored 17 on the MDS-UPDRS III, following a levodopa challenge he scored 9. He had no axial rigidity and the scores on the UPDRS mostly comprised that from abnormal posture (element 3.13, score = 4) and gait (element 3.10, score = 2) which are not necessarily parkinsonian-specific features. His camptocormia was slightly improved (TLF 'off' = $45^0$, TLF 'on' = $36^0$) but modest in comparison to the improvement in his other signs (e.g. bradykinesia and tremor).

## Patient five

This 72-year old man who was a keen marathon runner in his younger years (2-3 marathons per year) noted his right foot catching during training in his 40's. On occasion he also described his right leg rotating involuntarily and some months later experienced a sensation of a blow to the stomach as if he had been punched. After this episode he described feelings of being pulled forward and his trunk would flex forward repeatedly during a run. This jerky forward flexion continued occurring initially only on running, then when walking and even sometimes when he was standing. He saw various specialists and at the age of 57 he was diagnosed with axial dystonia, although there did not appear to be evidence of dystonia in his face, neck or limbs and DYT1 testing was negative. He tried various supportive spinal belts and was tried on various anticholinergic medication which were of no benefit. He had one course of botulinum toxin injections into his rectus abdominis without relief of his symptoms. His forward flexion got progressively worse (Video 7) although he had some relief when using a three-wheeled rollator. Aged 62 years he underwent deep brain stimulation to the pallidum and after some years he began to show improvement to his posture and the severity of the anterior axial flexion jerks (Video 7).

## Patient six

A 59-year old man with a long history of sciatica and low back pain (30 years) presented with a 2-year history of difficulty standing and walking upright without tremendous effort. He had previously undergone lumbar epidural, L4/5 decompression and a hip replacement for pain and felt his posture had deteriorated since these procedures. He described walking upright like holding a heavy weight for a prolonged period of time, which he could not sustain and therefore tended to stoop forward when walking. He used a stick for walking outdoors. He had no family history of neurological disorder. On examination he had full strength of all muscles tested including his neck, face and trunk extension from prone. Beevor's sign was absent and there was no evidence of muscle wasting. Rectus abdominis was tense on palpation when standing. There was no parkinsonism. He adopted an odd gait pattern when attempting to

overcome his flexed posture – he would extend his arms behind him and push out his chest inducing an exaggerated lumbar lordosis, he would then walk with jerks of his left shoulder and hip (Video 8). Investigations including MRI brain, CK, FSHD, *parkin* and LRRK2 genetic analyses were normal. EMG studies showed evidence of a chronic partial denervation in keeping with moderate lumbosacral polyradiculopathies (right tibialis anterior and gastrocnemius) but no evidence of a primary muscle or anterior horn cell disorder. Therapeutic interventions including trihexyphenidyl (not tolerated), a low slung backpack, walking poles and an off-the-shelf spinal brace gave short lived subjective benefit. He had no response to botulinum toxin injection to the rectus abdominis and ileopsoas. Intensive one-to-one physiotherapy sessions over an 11-week period improved his balance but did not improve his posture when walking; the therapist concluding that the overactivity of his hip flexors appeared to activate his trunk flexors in standing and walking. After review by spinal surgeons, movement disorder specialists, muscle specialists and various therapists it was felt that much of his overall problem was related to the degenerative spinal and subsequent orthopaedic mechanical alterations to his spine causing sagittal imbalance and his behavioural adaptation to them. He was advised to maintain an exercise program with stretches to counteract his truncal flexion.

## Patient seven

A 28 year old female was referred for investigation of her abnormal lateral spinal flexion deformity. She first developed right-sided pleuritic thoracic pain 5 years previously while sitting her final university exams. Shortly afterwards she noted her spine started to curve laterally. MRI brain and spine were reported as normal. The abnormal posturing relentlessly progressed and pain persisted, she described it worse when she was stressed and the pain and spinal curvature continued when she lay in bed at night. She was referred to orthopaedics who commented on her spinal curve being atypical for idiopathic adolescent/young adult scoliosis (there was no rotational component) and attempted spinal manipulation under general anaesthetic. An almost complete correction of her scoliotic deformity was achieved, but she was unable to tolerate the plaster cast due to breathlessness. Four years after onset she was referred to a movement disorder specialist for the consideration of a fixed truncal dystonia of unclear cause, query functional. Clinical examination revealed marked deformity of her posture with truncal shift to the left and a large thoracic curve (convex to the left) (Figure 23). Her left shoulder was elevated and her pelvis laterally tilted, higher on the right. Lateral flexion was only measured as $3^0$ from the vertical (therefore not qualifying as Pisa syndrome) likely due to the S-shaped nature of the curve. There was tenderness on palpation over the right chest wall and right shoulder tip with some hyperaesthesia and allodynia. There was no jerky movements, palpable spasms or co-contraction of agonist and antagonist muscle groups (paraspinals, rectus abdominis, latissimus dorsi) and no sensory *geste*. She did not have fixed knee or hip flexion contractures and her posture did not change with position (supine, sitting, standing, walking). Passive movement to the trunk to improve the posture was limited by pain. There was anisocoria (Dark: right 7mm, left 6mm; Bright light: right 4mm, left 3mm) and hyperhidrosis of the right hand and axilla. Neurophysiological studies including needle electromyography (EMG) was limited as the patient was unable to relax her thoracic and cervical paraspinal muscles completely but did not detect any abnormalities. Thermoregulatory sweat testing revealed profuse general sweating, but in the face and hand this was limited to the right side and associated with flushing and redness.

Despite previously “normal” whole spine imaging, the red flags of anisocoria and unilateral hyperhidrosis prompted further investigation with chest CT. A pericardial mass indenting the right atrium and distal SVC was identified. There was a number of metastatic lesions, lung parenchymal nodules extending into the pleura including the right posterior chest wall as well as a right subdiaphragmatic lesion. Histology revealed a neuroendocrine carcinoid tumour.

**Figure 23: Truncal shift and scoliosis due to intrathoracic malignancy**

Patient seven with spinal curvature, elevated left shoulder and tilted pelvis.

## Patient eight

A 45 year old man developed gradual lateral flexion of his head and trunk to the left following an episode of sudden mid-thoracic back pain aged 33 years. He described the initial pain as acute and 'searing' and took to his bed for several days. The pain became chronic as did his tendency to flex laterally soon after rising, associated with a sensation of pulling. He had no other medical conditions; there was no family history of neurological disorders. He was seen by various neurologists and spinal surgeons. Spinal and brain MR imaging was unremarkable. CK, copper studies and acanthocytes were normal/negative. He was given a trial of levodopa but without response. DYT1 testing was negative. He was diagnosed as axial dystonia and managed with anticholinergic medication and botulinum toxin injections although these produced no objective benefit to his posture. On examination seated or standing he had a laterally flexed head and neck (leftward) with chest protrusion and a prominent lumbar lordosis (Figure 24A&B). His posture was normal when supine or prone and with effort in front of a mirror he was able to correct his lateral flexion (Figure 24C). There was no tremor or jerking of his head or trunk and no hypertrophy in any cervical or paraspinal muscle group. He had a full range of movement in his neck (flexion, extension, side flexion and rotation) without evidence of weakness or rigidity. There was no parkinsonism and no focal neurological deficits. It was eventually considered he may have a functional axial dystonia.

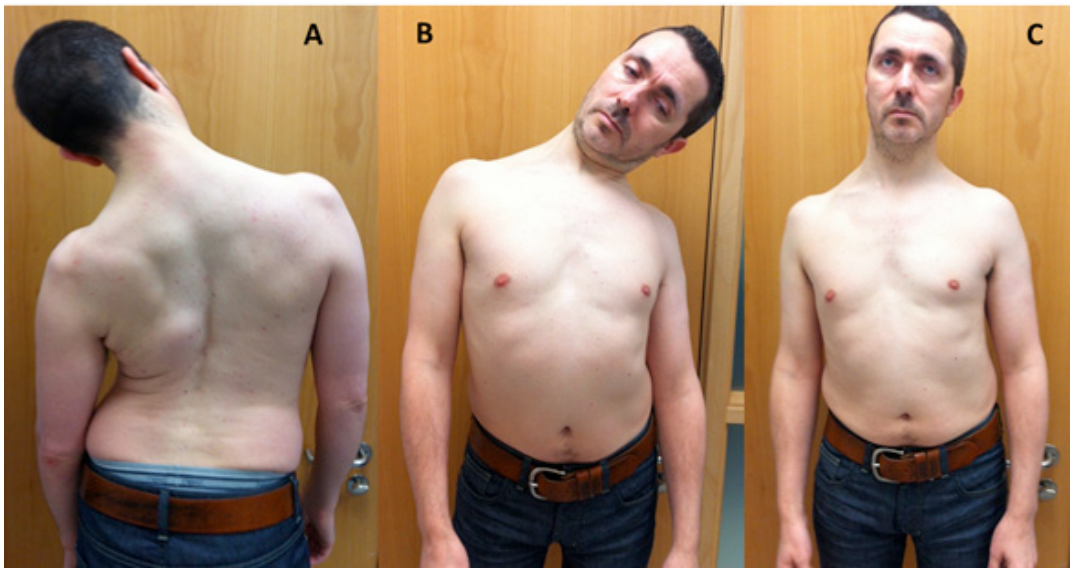



**Figure 24: Functional lateral flexion deformity**

Patient eight with mobile left lateral flexion deformity. Note the prominent lumbar lordosis and relatively straight spine with laterocollic posturing of the head and neck (A), chest protrusion (B) and almost complete improvement to midline with voluntary effort (C).

## Patient nine

This patient presented in his late 20's with onset of his trunk twisting to the right after a back injury and recurrent bouts of sciatica. His posture varied according to his level of pain. He was treated with a series of epidural anaesthetic injections which occasionally relieved his pain and postural deformity. He had no family history of movement disorder or neuromuscular disease and had never been exposed to neuroleptics drugs. He had a slightly waddling gait with an exaggerated lumbar lordosis, right lateral flexion and an elevated left shoulder. There was asymmetrical hypertrophy of his paraspinals (left>right). There was no focal dystonia of face, neck or limbs and no parkinsonism. He was considered to have either a possible primary axial dystonia or stiff person syndrome and underwent several further investigations. EMG including sampling of the paraspinal muscles was not suggestive of a myopathic process but the neurogenic changes in the right lower lumbar paraspinals were consistent with right-side sciatica, electrical silence was easily obtained and there was no continuous motor unit activity to suggest stiff person syndrome. Copper studies, anti-GAD antibodies and DYT1 gene analysis, MRI brain and spine were all normal/negative. He was started on trihexyphenidyl with possible response and made improvement over several years. After a strenuous bout of mountain biking his pain and posture deteriorated again requiring analgesia and rest. Over the course of 20 years he became aware of a pattern between excessive strenuous activity and worsening of his low back pain and lateral flexion posture. At review aged 41 years there was normal coronal balance, a mild lumbar scoliosis, no significant limitation to range of movement at the lumbar spine and no axial rigidity or cervical dystonia. His gait was normal and he was successfully weaned off trihexyphenidyl. It was felt likely his lateral flexion posture was developed to relieve his recurrent sciatic pain and the subsequent paraspinal spasm resulted in his mild lumbar scoliosis.

## *Discussion*

Patients 1, 2 and 4 highlight that FSHD may present not infrequently with camptocormia. FSHD is an autosomal dominant muscular dystrophy usually presenting at approximately 20 years of age. The genetic defect is a contraction of a 3.3kb microsatellite repeat (D4Z4) on the long arm of chromosome 4 (4q35). The repeat length in the unaffected population is greater than 11, but in patients with FSHD it is 1-10 units, and this is thought to lead to a toxic gain of function (van der Maarel et al, 2007, Lemmers et al, 2010). The number of D4Z4 repeats determines the severity of presentation and age of onset, and may relate to a specific phenotype, e.g. 1-3 repeats are associated with childhood onset and a more severe phenotype, 8-10 with a milder disease. Clinical diagnostic criteria often require the presence of weakness in the face or shoulder girdle at onset (Padberg et al, 1991). FSHD has recently been reported with localized paraspinal weakness, manifesting as camptocormia (Umapathi et al, 2002, Wood-Allum et al, 2004, Kottlors et al, 2010, Laroche and Cintas, 2010) and therefore should be considered even when there are no other signs of a myopathy and investigations are normal. Combining patients 1 and 2 with those previously reported, a Bln1-resistant fragment measuring between 30kb and 34kb equivalent to a repeat length of 9-10, appears consistent for this milder phenotype of late onset (Table 9).

| Author, year | Age | PC | Other signs | CK (U/L) | EMG | FH FSHD | 4q35 Bln1-rfs |
|---|---|---|---|---|---|---|---|
| Umpathi, 2002 | 55 F | cc | sw, fw, pw | 186 | myopathic | Yes | NK |
| Wood-Allum, 2004 | 66 M | cc | sw, fw, pw, pe | 294 | myopathic | No | 30kb |
| Kottlors, 2010 | 65 M | cc | ps atrophy | 45 | myopathic | Yes | 31kb |
| Patient one | 70 F | cc | mild pw, dc | 122 | normal | NK | 34kb |
| Patient two | 66F | cc | Mild pw & fw, dc | 183 | Not performed | Established after diagnosis | 34kb |

**Table 9: Cases of camptocormia due to FSHD**

Key: F female; M male; PC presenting complaint; cc camptocormia; sw scapular winging; fw facial weakness; dc décolletage sign; pw proximal weakness; pe pectus excavatum; ps paraspinal; CK creatine kinase; FH family history; rfs resistant fragment size; NK not known

Normal range for CK: 26-140IU/L

Several subtle clinical features in these cases hint at the underlying cause of the camptocormia. Mild muscle wasting such as the thinning of the upper fibres of pectoralis major, resulting in very prominent clavicles (we propose 'the décolletage sign' for this helpful pointer) should be looked for in suspected FSHD (Figure 22). Exposing the patient appropriately in order to observe the affected muscles for atrophy is essential, and examination of trunk extension is paramount not to miss weakness limited to the paraspinal muscles. Patients one and two compensated for their paraspinal weakness with extension of their arms held out behind their back, a posture that patients with camptocormia due to dystonia or Parkinson's rarely adopt. Careful observation of patients 1-3 while walking upright also show they tend to adopt hip extension to overcome their sagittal imbalance, something that distinguishes them from patients with camptocormia due to PD who due to tight hip flexion or contractures are unable to do. The patients with camptocormia due to myopathy were also able to overcome the bent spine posture with effort, long after its onset, whereas PD patients with camptocormia seem to have less capability to straighten themselves voluntarily as time passes. In patient 4 with concomitant Parkinson's disease and FSHD, the phenotype of the camptocormia was supportive of a myopathic aetiology. The modest improvement in thoracolumbar flexion following a levodopa challenge may suggest some impact from his Parkinson's disease but the mildness of his parkinsonism, severity of trunk extension weakness and supportive EMG findings were more convincing of myopathy. The onset of forward flexion predated his Parkinson's symptoms (PD related camptocormia usually occurs several years into the disease) and the full reversibility of camptocormia when supine is also supportive of a muscular dystrophy aetiology rather than PD. Subtle head drops were noted in patient two and three suggestive of possible neck extension weakness. The 'head drop' sign has recently been described in Neuroacanthocytosis (NA) (Chorea-Acanthocytosis (Schneider et al, 2010) and McLeod syndrome (Chauveau et al, 2011)), and also in Huntington's disease (Spampinato et al, 2013). The movements causing the head drop have variously been proposed to be myoclonic, tic-like, choreic or dystonic in nature (Schneider et al, 2010). In the patients described above the head drops are likely to be myopathic in origin and caution is again advised against overdiagnosis of subtle postural movements as purely extrapyramidal in origin. The phenotype of the head drops in these cases was certainly different to those observed

in NA and HD in that they were more subtle and less violent.

The sensory trick or *geste antagoniste* describes a manoeuvre adopted by a patient to overcome an abnormal posture due to dystonia. The most common example is a patient with torticollis (cervical dystonia) moving their hand to touch a particular point on their chin to correct their abnormal head position. This study has described 4 patients with camptocormia due to muscle disease (1-4) who all adopted tricks to help them walk with straighter posture and one patient with presumed dystonic camptocormia (patient 5) who did not. These cases illustrate the difficulty in distinguishing between a *geste antagoniste*, and compensatory movements made to overcome weakness or pain. In cases 1 and 2, the presentation of camptocormia with manoeuvres which were not sensory tricks were misconstrued as idiopathic axial dystonia (Bhatia et al, 1997). Patient five had a marked jerky component to his camptocormia as is reported in primary dystonic camptocormia and is not seen in camptocormia due to muscle disease or Parkinson's disease (Bhatia et al, 1997).

Distinguishing between structural, musculoskeletal, antalgic and functional postural deformity can be extremely difficult as cases 5 and 7-9 illustrate. Patient five developed camptocormia post lumbar decompression and hip replacement which may reflect a biomechanical shift of spinopelvic alignment. Patients eight and nine fell into a similar category of potential alterations of body schema due to central remodelling due to pain. They gave a clear history of back pain or injury inducing the abnormal posture. A functional adaptation due to chronic pain ('habitual antalgic posturing') may be a more appropriate title than peripheral or secondary dystonia as has been suggested in some of these cases. All were diagnosed with probable primary axial dystonia for long periods of time when other investigations were not forthcoming despite the absence of clear neurophysiological evidence to support this diagnosis. On the other hand patient seven with a marked scoliotic posture resulting from a mediastinal mass was presumed due to a functional cause and remained undiagnosed for over 5 years. The delay in diagnosis may in part have been due to the fact that the patient was a young female, onset had occurred during a period of stress (exams), and early investigations by a neurologist had been unremarkable. The static nature of the curvature (unchanging with effort or position) and the lack of spread (of 'dystonia') to other body parts made it unusual for

young onset primary dystonia. The pleuritic type pain, anisocoria and hemi hyperhidrosis were early missed pointers to an underlying intrathoracic structural lesion. The association of thoracic malignancy with sympathetic neurological complications, especially Horner's syndrome is well recognised, particularly in the case of tumours occurring at the thoracic inlet. Unilateral sweating is however a rare phenomenon but should raise suspicion of compressive lesions in this area (Wang et al, 1981, Lindsay et al, 1986). These cases reinforce the view that abnormal posture alone is insufficient to diagnose dystonia. Supportive features of dystonia such as observation and palpation for active muscle spasms, hypertrophied muscle groups, a limited range of movement about the affected area and associated jerking (dystonic tremor) should be sought.

## *Conclusion*

Isolated camptocormia may receive different diagnoses and be interpreted differently by various hospital specialists; some looking upon it as a myopathy while others considering it to be a flexion dystonia. A compensatory manoeuvre for weakness or pain can be mistaken for a *geste antagoniste* resulting in a diagnosis of dystonia in specialist movement disorder clinics when myopathy is less frequently encountered and clinical features are subtle. Study of these patients emphasises that abnormal posture alone is insufficient for a diagnosis of dystonia and one should perhaps be more reserved in use of this diagnosis. The following pointers may help in the diagnosis of isolated camptocormia presenting to neurologists and similar advice can be given for other abnormal postures like Pisa syndrome, compensated spinal curvature and dropped head syndrome that are frequently referred to movement disorder and muscle clinics.

**Features of camptocormia suggestive of muscle disease:-**

- Flexion advancing with increasing distance walked – fatiguing (also seen in PD)
- Hip extension, arms held extended behind (may be locked) or pressing down on thighs when attempting to walk straighter
- No response or worsening with 'dystonia' treatments
- Patients describe overcoming the posture as 'effortful or exhausting'
- Unable to extend trunk from the prone position and other signs of core muscle weakness (e.g. Gower's manoeuvre)

**Features of camptocormia suggestive of dystonia:-**

- Patient may complain of cramps, pulling or spasms in affected muscles
- May be associated jerking of affected region - flexion spasms (Bhatia et al, 1997), or dystonic posturing elsewhere
- Abnormal posture is not distance dependent, tends not to 'fatigue'
- May respond to botulinum toxin therapy or pallidal DBS

**Features suggestive of parkinsonian camptocormia:-**

- Gradual or subacute onset usually several years after diagnosis of Parkinson's disease with progressive worsening
- Patient rarely gives history of sensory *geste* or particular manoeuvre to overcome postural deformity
- Posture may be partially fixed with hip and knee flexion contractures developing

**Features of camptocormia suggestive of musculoskeletal or functional disorder:-**

- Often a history of injury, trauma, pain or surgical procedure at onset of abnormal posture
- Often of acute or subacute onset then static or fluctuating with paroxysms related to pain
- No restriction of passive movement unless chronic and has developed contractures

# Chapter 6: Conclusions

Postural deformities are frequent and disabling complications of Parkinson's disease and atypical parkinsonism. They include camptocormia, antecollis (dropped neck), Pisa syndrome and scoliosis. Following review of the literature and findings from this study we propose that the deformities in PD patients result from the interplay of multiple, complex factors. Important pathological changes may lie within the basal ganglia and its connections giving rise to muscular rigidity, loss of postural reflexes and axial dystonia. Development of disproportionate postural deformity may necessitate either a second hit or an additional acquired risk factor, such as myopathy (probably due to disuse in PD), body scheme defects due to centrally impaired proprioception and structural changes in the biomechanics of the spine.

## *Summary of study findings*

From the aims initially set out in the introductory chapter, this study has identified shortcomings of the current definitions of both camptocormia and Pisa syndrome, found an association between axial predominant PD and severity of postural deformity, confirmed the suspicion that PD-related postural deformity is not immediately responsive to dopaminergic therapy and shown that it differs from age-related degenerative spinal disease.

From clinical examination we established that the majority of patients have persistence of their postural abnormalities when supine or seated, and these postural deformities are not fully reversible when the patient is recumbent. When the deformity is reversible this may reflect very recent onset of deformity (or a young and supple patient), or that another process entirely is causative of the posture (e.g. concomitant FSHD or osteoporotic vertebral collapse).

We recommend that one should be vigilant for postural deformity in any patients with an axial akinetic rigid/PIGD subtype. This has been proposed as a risk factor by other small studies (Lepoutre et al, 2006, Bloch et al, 2006) and we also found a significant

correlation between this PD subtype and postural deformity in our clinical and radiological studies.

While it is tempting to increase dopaminergic medication in patients with progression of disease associated with deterioration of posture, this study has shown that in those with recognised postural deformity of 5 years or more duration, increasing PD medication does not improve posture.

While this study does not answer the burning question of whether the prime insult in PD deformity is dystonia or myopathy, it suggests that this shouldn't be the only debate. Radiological study was chosen in order to ascertain if PD-related deformities were simply reflective of accelerated aging or reflected a unique process, which may provide clues to the underlying pathogenesis. This study has shown that PD-related postural deformity is not the same as de novo degenerative scoliosis or kyphosis of pure adult deformity. The overwhelming feature of spinal deformity in PD is collapse. Both in coronal and sagittal plane deformity the standing imaging was remarkable for the severe failure against gravity – a feature distinguishing PD deformity from that of adults with 'de novo' degenerative deformity without PD. This lack of effective compensatory response (e.g. S-shaped curves to bring patient back to midline in Pisa syndrome, hip or thoracic extension in camptocormia) was consistent and was characteristic of PD related deformity. This trait suggests that awareness of trunk position in space is very impaired and strengthens the arguments that proprioceptive deficits are a large contributor to the deformity and should be a target for future research.

## *Directions for future research*

The lack of awareness of the visual vertical and the impairment of axial proprioception, which has been described in patients with PD (Wright et al, 2010), needs examined in PD patients with postural deformity. If these impairments are more significantly affected compared to a PD control group (no postural deformity) it is suggestive of an important mechanism in deformity development.

One short falling of this study was the lack of a non-postural deformity PD control group. Case-control study comparing disease characteristics, medical history and clinical examination findings may have heralded relevant risk factors for postural deformity development. Back pain, sciatica, previous hip fracture, vertebral disc prolapse, medication use, physiotherapy access, level of exercise/general fitness and spinal shape may be a few of the possible determinants of those PD patients who may be at greater risk. A prospective longitudinal study with long term follow up of a cohort of PD patients may highlight potential factors related to deformity development in PD patients.

Establishing better understanding of the aetiology of postural deformity development in PD is clearly paramount but while studies continue, developing potential therapies should not wait. In the following section we suggest areas that have potential to treat these disabling phenomenon and may be worthy of larger trials.

### *Directions for managing postural deformity in PD*

While secondary or co-incidental features such as osteoporotic collapse, spondylolisthesis and osteophytosis will result in changes to the skeletal shape and may render late intervention less effective, the key obstacle in reversing postural deformity is preventing reaching the 'tipping point' at which gravity can no longer be conquered. During the progression of any sagittal plane deformity, malalignment may be offset by the spinopelvic compensatory mechanisms until they have been used to their full potential, after which point further kyphosis results in decompensated sagittal spinal alignment and gravity is simply too much to overcome. The muscles and ligaments will have overstretched, the new alignment of paraspinal muscles will hinder or completely alter their function, and the spine is then said to have failed. At this point conservative intervention is extremely unlikely to help, i.e. we need to detect and treat patients early.

While physical exercise and targeted physiotherapy are important measures in combating postural disturbance, freezing episodes and falls in Parkinson's disease (Goodwin et al, 2008, Tomlinson et al, 2010), evidence for a role for physical

interventions in postural deformity is lacking. The following knowledge gained from patients and the findings of the studies performed may help direct future research.

Many of the patients enrolled in this study had searched for or manufactured their own aids or adaptations to render walking, sitting or other activities easier. An electronics engineer with PD who had moderate TLF fashioned himself a tilt switch activated alarm which alerted him when his posture deteriorated. The auditory signal acted as a cue for him to straighten his posture when he involuntarily bent beyond a pre-set angle. He had researched his idea and adapted it from a case reporting a good outcome in a patient with chronically stooped posture of presumed functional basis (Tiller et al, 1982). Video 9 shows the patient wearing the alarm system and demonstrating how it works depending on his angle of anterior flexion. Unfortunately he found that he was not always able to maintain as good an angle as he desired and the noise from the alarm started to irritate him. This is in keeping with the observation that better reward than punishment learning occurs in PD patients in their 'on' medication state (Frank et al, 2004). A less aversive stimulation focussed on reinforcing good posture or trialling in less severely affected patients may produce better results and is worthy of further study.

Impaired proprioception as maybe suggested by the impaired trunk extension from the prone position in the absence of weakness and the difficulty using the appropriate muscles effectively to 'stand up straight' may be a potential mechanism to target. The 'Lee Silverman Voice Treatment BIG (LSVT BIG)' style of exercise-based behavioural therapy utilises the principle of repetitive large amplitude movements (Fox et al, 2012). The technique is thought to work via cueing ("bigger movements") to drive greater motor output and increase the amplitude of the resulting movement. Movement is performed in an intensive effortful manner which it is hoped will promote activity-dependent neuroplasticity and when practiced regularly to lead to recalibration of the PD patients motor and perceptual systems. This is then incorporated into daily activities in an attempt to ingrain it as a habit. A small study has reported good outcomes in walking speed and reaching movements (Farley and Koshland, 2005) and it would be interesting to test it as an intervention in those with postural deformity and axial predominant PD who may have significant kinaesthetic impairment.

Another technique to target muscles which the patient appears to have difficulty recruiting is functional electrical stimulation (FES). If patients have difficulty recruiting their lumbar paraspinals it is possible to directly stimulate these muscles to contract. FES of the paraspinal muscles is a complex intervention (Medical Research Council, 2000) with possible active ingredients including both direct muscle activation and increased sensory input. In one patient with PD and moderate TLF continuous 40Hz stimulation was applied to the lumbar paraspinals bilaterally but did not produce any objective improvement to TLF (at tolerable levels of stimulation) when walking. Concurrent stimulation of the lumbar paraspinals and the gluteus maximus produced an improvement to TLF, but this was not tolerated at any length by the patient because the continuous stimulation hampered normal walking. A second patient was trialled using the Odstock Dropped Foot Stimulator (ODFS) for the purpose of the heel switch triggering stimulation to the gluteus maximus only at the heel strike phase of the gait cycle. An objective improvement to TLF angle was not demonstrated but the patient did report and subjectively showed a more fluid gait pattern. It is possible that direct stimulation of the gluteal muscles helped stabilise her pelvis and permitted an 'unlocking' of her pelvic and shoulder girdle which had been held 'en bloc' prior to stimulation. With the stimulation switched on she showed a somewhat less rigid gait with improved arm swing. FES has been shown to assist gait in a small pilot study of PD patients (Mann et al, 2008). Stimulation of the gluteal muscles may be a more appropriate target in future studies than the common peroneal nerve used in this study.

Extrapolating the radiological findings to treatments for camptocormia and Pisa syndrome also suggests therapy should target the gluteal muscles which act to ensure a good lumbar lordosis, early in the course of PD. Focus should also be placed on preventing hip flexion tightening and contractures which limits potential compensation to sagittal imbalance by restricting pelvic retroversion. Walking backwards is a simple technique which requires effective hip extension. Some PD patients with camptocormia report walking backward as a trick they have discovered for walking straighter, and it is often also indiscriminately labelled as a sensory *geste*. In those without fixed contractures, activity incorporating backward walking may help lengthen the hip flexors which are shortened in PD due to the propensity to stoop forward. Video 10

demonstrates a young-onset PD patient with camptocormia with improved sagittal plane alignment when walking backwards. Walking backwards has been incorporated into rehabilitation programmes to good effect in patients post-stroke (Yang et al, 2005), and has been examined in PD patients but not with specific regard to improving posture (Hackney and Earhart, 2009). Encouraged by the results of the paper demonstrating good outcomes in PD patients with camptocormia utilising the principle of thoraco-pelvic anterior distraction (TPAD) to induce a lumbar lordosis (de Seze et al, 2008), two patients were fitted and supplied with a TPAD device. Unfortunately both found the orthotic brace uncomfortable and restrictive, one describing it as "almost suffocating" which precluded her wearing it sufficiently to assess benefit. One patient had a change in body weight (gain) which meant that by the time the custom-made device arrived in London it was no longer sitting on his hips and utilising his pelvis as a base of support. Instead it sat higher on his torso and with the lack of pelvic stabilisation he was still able to flex at the thoracolumbar junction, the added weight of the device causing his angle of TLF to increase.

The large collapse element of the deformity which the radiological study found characteristic of Parkinson-related deformity may be overcome with use of high framed walking devices which encourage erect posture. A small case series of PD patients with camptocormia followed for just 3-7 days described improved standing and walking height with a high-framed forearm walker (Schroeteler et al, 2011). Three patients in this study borrowed the high-framed wheeled walker for a period of 6 weeks for daily use. While the benefit to height and posture could immediately be observed (Video 11), goal attainment, back pain, 10m walking speed and both sagittal and coronal alignment (as measured using TLF and LF angles) did not.

The spectrum of deformities highlighted by this clinical study and the varying presentations within each deformity subtype renders interventional study difficult and means that treatment for these disabling and drug refractory phenomenon is likely to be based on small case series, single reports and clinician and patient experience. Taking into account not only less effective truncal muscle function, but also impaired kinaesthesia and spinal biomechanics will be paramount to our full understanding of postural deformity in PD and should help focus treatment trials. Therapeutic techniques

such as functional electrical stimulation (McQuain et al, 1993) or proprioceptive reinforcement using lumbar supports or approaches analogous to LSVT BIG may have a role in the control of the collapse element of PD deformities. Mobility around the axial skeleton suggests muscle and balance retraining, such as tailored posture manipulative physiotherapy and focussed exercises (Negrini et al, 2008, Bartolo et al, 2010), Alexander technique, pilates, yoga, Tai Chi, perhaps combined with the use of spinal orthotics (de Seze et al, 2008) might be helpful in improving the reducible axial changes, but only before the spinal elements have failed.

# Appendices

Appendix 1 – Clinical Examination proforma

Appendix II – MDS-UPDRS score sheet

## Appendix I

## Clinical Examination Proforma

- Participant ID code:
- MDS-UPDRS part III score:
- H&Y stage:

Standing examination

- Observe standing and walking, what is main postural deformity:-

  Camptocormia/Pisa syndrome/Mixed/Stooped/Antecollis

  Secondary features:

- Flatback? Y/N
- Compensatory cervical hyperlordosis? Y/N
- Pelvic tilt? Y/N Which side down?
- Trendelenberg's sign? Y/N Which side dropped on elevation
- Unequal shoulder height? Y/N Which side down?
- Knees bent? Y/N Which side most?
- Any muscle atrophy/hypertrophy?

  Y/N……

- Any Myogelosis (knots), rib humps or loin humps? Y/N
- Any active spasms/jerks/paradoxical muscle activity?

  Y/N……

  (Rectus Abdominis, Lumbar paraspinals, Thoracic paraspinals, quadriceps, latissimus dorsi, etc)

- Any sensory gestes / manoeuvres to aid correction of posture? Y/N

- Sagittal balance (C7-wall distance)

  Off: usual best

  On: usual best

- Thoracolumbar flexion (angle b/n vert + line through sacrum and C7)

  Off: usual best

  On: usual best

- Coronal imbalance (C7 – intergluteal cleft distance)

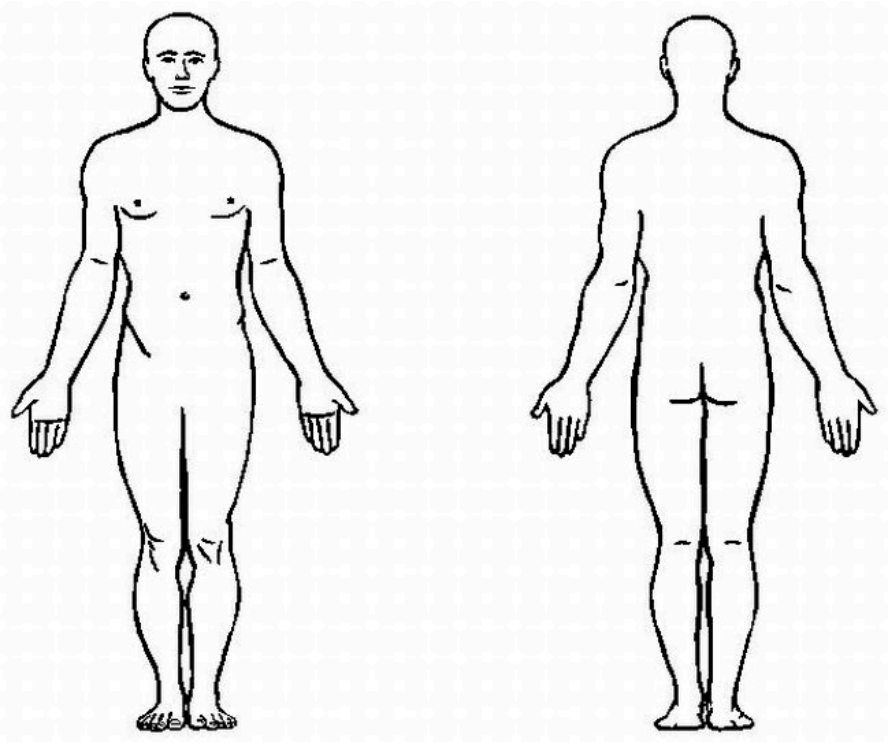
  Off: usual best

  On: usual best

- Lateral flexion (angle b/n vert + line through sacrum and C7)

  Off: usual best

  On: usual best



Seated examination

- Posture with legs unsupported (edge of couch) with eyes open and closed

- Prayer sign/Trigger finger/Dupuytren's contracture? Y/N
- Any other joint deformity? Y/N

Supine examination

- Coronal/lateral deformity resolved/persistent
- Sagittal/Anterior deformity resolved/persistent
- If persistent, where is site of impaired reversibility?

- Strength testing
    - NE
    - NF
    - UL
    - LL
    - TE (from prone)
    - HE (from prone)
    - Beevors sign?
- Limitation to Straight Leg Raise? Y/N Side R/L/Both
- Fixed hip flexion deformity on Thomas' test? Y/N
- Fixed knee flexion deformity? Y/N

# Appendix II

| Patient Name or Subject ID | Site ID | (mm-dd-yyyy) Assessment Date | Investigator's Initials |
|---|---|---|---|
| _____ | ____ ____ ____ | ___ ___ - ___ ___ - ___ ___ ___ ___ | ____ ____ ____ |

**MDS UPDRS Score Sheet**

| | | | | | |
|---|---|---|---|---|---|
| 1.A | Source of information | ☐ Patient ☐ Caregiver ☐ Patient + Caregiver | 3.3b | Rigidity– RUE | |
| | | | 3.3c | Rigidity– LUE | |
| **Part I** | | | 3.3d | Rigidity– RLE | |
| 1.1 | Cognitive impairment | | 3.3e | Rigidity– LLE | |
| 1.2 | Hallucinations and psychosis | | 3.4a | Finger tapping– Right hand | |
| 1.3 | Depressed mood | | 3.4b | Finger tapping– Left hand | |
| 1.4 | Anxious mood | | 3.5a | Hand movements– Right hand | |
| 1.5 | Apathy | | 3.5b | Hand movements– Left hand | |
| 1.6 | Features of DDS | | 3.6a | Pronation- supination movements– Right hand | |
| 1.6a | Who is filling out questionnaire | ☐ Patient ☐ Caregiver ☐ Patient + Caregiver | 3.6b | Pronation- supination movements– Left hand | |
| | | | 3.7a | Toe tapping–Right foot | |
| 1.7 | Sleep problems | | 3.7b | Toe tapping– Left foot | |
| 1.8 | Daytime sleepiness | | 3.8a | Leg agility– Right leg | |
| 1.9 | Pain and other sensations | | 3.8b | Leg agility– Left leg | |
| 1.10 | Urinary problems | | 3.9 | Arising from chair | |
| 1.11 | Constipation problems | | 3.10 | Gait | |
| 1.12 | Light headedness on standing | | 3.11 | Freezing of gait | |
| 1.13 | Fatigue | | 3.12 | Postural stability | |
| **Part II** | | | 3.13 | Posture | |
| 2.1 | Speech | | 3.14 | Global spontaneity of movement | |
| 2.2 | Saliva and drooling | | 3.15a | Postural tremor– Right hand | |
| 2.3 | Chewing and swallowing | | 3.15b | Postural tremor– Left hand | |
| 2.4 | Eating tasks | | 3.16a | Kinetic tremor– Right hand | |
| 2.5 | Dressing | | 3.16b | Kinetic tremor– Left hand | |
| 2.6 | Hygiene | | 3.17a | Rest tremor amplitude– RUE | |
| 2.7 | Handwriting | | 3.17b | Rest tremor amplitude– LUE | |
| 2.8 | Doing hobbies and other activities | | 3.17c | Rest tremor amplitude– RLE | |
| 2.9 | Turning in bed | | 3.17d | Rest tremor amplitude– LLE | |
| 2.10 | Tremor | | 3.17e | Rest tremor amplitude– Lip/jaw | |
| 2.11 | Getting out of bed | | 3.18 | Constancy of rest | |
| 2.12 | Walking and balance | | | Were dyskinesias presen | ☐ No ☐ Yes |
| 2.13 | Freezing | | | Did these movements interfere with ratings? | ☐ No ☐ Yes |
| 3a | Is the patient on medication? | ☐ No ☐ Yes | | Hoehn and Yahr Stage | |
| 3b | Patient's clinical state | ☐ Off ☐ On | **Part IV** | | |
| 3c | Is the patient on Levodopa? | ☐ No ☐ Yes | 4.1 | Time spent with dyskinesias | |
| 3.C1 | If yes, minutes since last dose: | | 4.2 | Functional impact of dyskinesias | |
| **Part III** | | | 4.3 | Time spent in the OFF state | |
| 3.1 | Speech | | 4.4 | Functional impact of fluctuations | |
| 3.2 | Facial expression | | 4.5 | Complexity of motor fluctuations | |
| 3.3a | Rigidity– Neck | | 4.6 | Painful OFF-state dystonia | |

# List of supplementary videos

Video 1

Chapter 2: PD patient with camptocormia arising from chair, walking and attempting to stand up straight with minimal improvement to his posture.

Video 2

Chapter 2: PD patient with Pisa syndrome walking when ‘off’ and then ‘on’ medication.

Video 3

Chapter 5: Patient 1 (Part 1 - 2005) abnormal standing posture and camptocormic gait. (Part 2 - 2010) exhibiting camptocormia when walking; walking erect with arms extended and hands locked behind back; attempting trunk extension from prone position; difficulty sitting up from supine position; absent Beevor’s sign (Beevor’s sign is the headward deviation of the umbilicus on neck flexion resulting from weakness of the lower rectus abdominus, the patient is asked to flex her neck by putting her chin on her chest, her umbilicus does not move toward her head. Beevor’s sign is described in spinal cord injuries (T10-12) and in typical FSHD).

Video 4

Chapter 5: Patient 2 walking comfortably exhibiting mild camptocormia, then with great effort attempting to walk with erect posture.

Video 5

Chapter 5: Patient 3 walking unaided and then with walking poles and then getting up from the floor utilizing Gower’s manoeuvre.

Video 6

Chapter 5: Patient 4 walking with hands pressed on thighs and exhibiting failure of

trunk extension from the prone position.

Video 7

Chapter 5: Patient 5 with dystonic camptocormia walking and standing at rest, note the prominent flexion jerks (part one). Several years following pallidal DBS there is remarkably less frequent or violent axial flexion jerks (part two).

Video 8

Chapter 5: Patient 6 with camptocormia walking normally and then attempting to walk taller. To compensate he pushes his chest forward and jerks his left shoulder.

Video 9

Chapter 6: Parkinson's patient with camptocormia demonstrating self-manufactured tilt-switch alarm device for monitoring angle of flexion.

Video 10

Chapter 6: Young-onset Parkinson's patient with camptocormia when walking forwards, with improved posture when walking backwards.

Video 11

Chapter 6: PD patient with camptocormia walking unaided, with a low-level rollator frame and with a high-framed walking device demonstrating improvement to posture.

# Acknowledgements

My warmest thanks and a huge debt of gratitude go to Professor Andrew Lees who gave me the opportunity to carry out this clinical research and entrusted me with attempting all I could think of to 'straighten up' his patients. My time spent studying this area (and a few others) during my research period has been the major highlight of my professional life to date and I will never forget my time spent at the Reta Lila Institute and The National Hospital for Neurology under Prof's tutelage. The pearls of Movement Disorder wisdom from his vast experience will be passed onto all I teach in the years to come in this, the most fascinating of the Neurology subspecialties.

Thanks also go to those who worked closely with me on the main studies in this thesis – especially Dr Laura Silveira-Moriyama, Dr Indran Davagnanam, Mr Sean Molloy and Glenn Nielsen. Whose advice, discussions and teaching have been essential to putting together this work. I really appreciate how generously you all gave of your time and experience.

Those other Lees' fellows that I have worked beside and who have made my time at Queen Square so enjoyable include Dr Helen Ling, Dr Alastair Noyce, Dr Atbin Djamshidian, Dr Nadia Magdalinou, Dr Sean O'Sullivan and Dr Luke Massey. I was made to feel so welcome when I arrived and have made lifelong friendships over the past few years. I would like to single out Dr Atbin Djamshidian for being particularly helpful and giving of his time in steering me through the final stages of formatting this thesis – your help is massively appreciated especially with my very tight deadline! You have all been so kind to me and made this adventure hugely enjoyable.

I also wish to thank Karen Shaw, Iliyana Komsiyska, Cathy Magee, Katia Matthews Cherry James and Susan Stoneham. Friends and colleagues who have helped in various ways over the years and it has been a pleasure to work with.

This research was only possible due to the generosity of the patients involved. They gave of their time, energy and personal experience and I hope that continued research in this area will one day benefit them. The trustees of the Reta Lila Weston Institute and

Parkinson’s UK generously supported this research.

Finally I am indebted to my family and especially Aidan, who have supported me endlessly in this and all aspects of life.

# Bibliography


Abe K, Uchida Y & Notani M. 2010. Camptocormia in Parkinson's disease. *Parkinsons Dis,* (Article ID 267640)**,** 1-5.

Agari T & Date I. 2012. Spinal cord stimulation for the treatment of abnormal posture and gait disorder in patients with Parkinson's disease. *Neurol Med Chir,* 52(7)**,** 470-4.

Allert N, Miskiewicz A & Coenen V. 2011. [Deep brain stimulation for Parkinson's disease and camptocormia? A case report]. *Fortschr Neurol Psychiatr,* 79(2)**,** 97-101.

Asahi T, Taguchi Y, Hayashi N, et al. 2011. Bilateral subthalamic deep brain stimulation for camptocormia associated with Parkinson's disease. *Stereotact Functional Neurosurg,* 89(3)**,** 173-7.

Ashour R & Jankovic J. 2006. Joint and skeletal deformities in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Mov Disord,* 21(11)**,** 1856-63.

Ashour R, Tintner R & Jankovic J. 2005. Striatal deformities of the hand and foot in Parkinson's disease. *Lancet Neurol,* 4(7)**,** 423-31.

Azher S & Jankovic J. 2005. Camptocormia: pathogenesis, classification, and response to therapy. *Neurology,* 65(3)**,** 355-9.

Babat L, McLain R, Bingaman W, et al. 2004. Spinal surgery in patients with Parkinson's disease: construct failure and progressive deformity. *Spine (Phila Pa 1976),* 29(18)**,** 2006-12.

Baik J, Kim J, Park J, et al. 2009. Scoliosis in patients with Parkinson's disease. *J Clin Neurol,* 5(2)**,** 91-4.

Bartolo M, Serrao M, Tassorelli C, et al. 2010. Four-week trunk-specific rehabilitation treatment improves lateral trunk flexion in Parkinson's disease. *Mov Disord,* 25(3)**,** 325-31.

Beevor C. 1904. *The Croonian Lectures on Muscular Movements and Their Representation in the Central Nervous System Delivered before The Royal College of Physicians of London June 1903,* London, Adlard and Son.

Berven S & Lowe T. 2007. The Scoliosis Research Society classification for adult spinal deformity. *Neurosurg Clin N Am,* 18(2)**,** 207-13.

Bhatia K, Quinn N & Marsden C. 1997. Clinical features and natural history of axial predominant adult onset primary dystonia. *J Neurol Neurosurg Psychiatry,* 63(6)**,** 788-91.

Bhattacharya K, Giannakikou I, Munroe N, et al. 2000. Primary anticholinergic-responsive Pisa syndrome. *Mov Disord,* 15(6)**,** 1285-7.

Birknes J, White A, Albert T, et al. 2008. Adult degenerative scoliosis: a review. *Neurosurgery,* 63(3 Suppl)**,** 94-103.

Bloch F, Houeto J, Tezenas du Montcel S, et al. 2006. Parkinson's disease with camptocormia. *J Neurol Neurosurg Psychiatry,* 77(11)**,** 1223-8.

Bloem B, Beckley D & van Dijk J. 1999. Are automatic postural responses in patients with Parkinson's disease abnormal due to their stooped posture? *Exp Brain Res,* 124(4)**,** 481-8.

Boesch S, Wenning G, Ransmayr G, et al. 2002. Dystonia in multiple system atrophy. *J Neurol Neurosurg Psychiatry,* 72(3)**,** 300-3.

Bonanni L, Thomas A, Varanese S, et al. 2007. Botulinum toxin treatment of lateral axial dystonia in Parkinsonism. *Mov Disord,* 22(14)**,** 2097-103.

Bonneville F, Bloch F, Kurys E, et al. 2008. Camptocormia and Parkinson's disease: MR imaging. *Eur Radiol,* 18(8)**,** 1710-9.

Bourghli A, Guerin P, Vital J, et al. 2012. Posterior spinal fusion from T2 to the sacrum for the management of major deformities in patients with Parkinson disease: a retrospective review with analysis of complications. *J Spinal Disord Tech,* 25(3)**,** E53-60.

Broussolle E, Krack P, Thobois S, et al. 2007. Contribution of Jules Froment to the study of parkinsonian rigidity. *Mov Disord,* 22(7)**,** 909-14.

Burleigh A, Horak F, Nutt J, et al. 1995. Levodopa reduces muscle tone and lower extremity tremor in Parkinson's disease. *Can J Neurol Sci,* 22(4)**,** 280-5.

Cannas A, Solla P, Floris G, et al. 2005. Reversible Pisa syndrome in Parkinson's disease during treatment with pergolide: a case report. *Clin Neuropharmacol,* 28(5)**,** 252.

Cannas A, Solla P, Floris G, et al. 2009. Reversible Pisa syndrome in patients with Parkinson's disease on dopaminergic therapy. *J Neurol,* 256(3)**,** 390-5.

Capelle HH, Schrader C, Blahak C, et al. 2010. Deep brain stimulation for camptocormia in dystonia and Parkinson's disease. *J Neurol,* 258(1)**,** 96-103.

Carpenter MG, Allum JH, Honegger F, et al. 2004. Postural abnormalities to multidirectional stance perturbations in Parkinson's disease. *J Neurol Neurosurg Psychiatry,* 75(9)**,** 1245-54.

Carpenter MG & Bloem BR. 2010. Postural control in Parkinson patients: A proprioceptive problem? *Exp Neurol,* 227(1)**,** 26-30.

Charpentier P, Dauphin A, Stojkovic T, et al. 2005. [Parkinson's disease, progressive lumbar kyphosis and focal paraspinal myositis]. *Rev Neurol (Paris),* 161(4)**,** 459-63.

Chauveau M, Damon-Perriere N, Latxague C, et al. 2011. Head drops are also observed in McLeod syndrome. *Mov Disord,* 26(8)**,** 1562-3.

Cobb J. 1948. Outline for the study of scoliosis. *In:* Edwards, J (ed.) *American Academy of Orthopaedic Surgeons, Instructional course lectures.* Ann Arbor.

Colosimo C & Salvatori FM. 2009. Injection of the iliopsoas muscle with botulinum toxin in camptocormia. *Mov Disord,* 24(2)**,** 316-7.

Cropp CD, Yee SW & Giacomini KM. 2008. Genetic variation in drug transporters in ethnic populations. *Clin Pharmacol Ther,* 84(3)**,** 412-6.

Danneels LA, Cagnie BJ, Cools AM, et al. 2001. Intra-operator and inter-operator reliability of surface electromyography in the clinical evaluation of back muscles. *Man Ther,* 6(3)**,** 145-53.

de Seze M, Creuze A, de Seze M, et al. 2008. An orthosis and physiotherapy programme for camptocormia: a prospective case study. *J Rehabil Med,* 40(9)**,** 761-5.

Di Matteo A, Fasano A, Squintani G, et al. 2011. Lateral trunk flexion in Parkinson's disease: EMG features disclose two different underlying pathophysiological mechanisms. *J Neurol,* 258(5)**,** 740-5.

Djaldetti R, Mosberg-Galili R, Sroka H, et al. 1999. Camptocormia (bent spine) in patients with Parkinson's disease--characterization and possible pathogenesis of an unusual phenomenon. *Mov Disord,* 14(3)**,** 443-7.

Doherty KM, Silveira-Moriyama L, Parkkinen L, et al. 2013. Parkin disease: a clinicopathologic entity? *JAMA Neurol,* 70(5)**,** 571-9.

Dubois B, Slachevsky A, Litvan I, et al. 2000. The FAB: a Frontal Assessment Battery at bedside. *Neurology,* 55(11)**,** 1621-6.

Dupeyron A, Stober N, Gelis A, et al. 2010. Painful camptocormia: the relevance of shaking your patient's hand. *Eur Spine J,* 19 (Suppl 2)**,** S87-90.

Duval-Beaupere G, Lespargot A & Grossiord A. 1985. Flexibility of scoliosis. What does it mean? Is this terminology appropriate? *Spine,* 10(5)**,** 428-32.

Duvoisin RC & Marsden CD. 1975. Note on the scoliosis of Parkinsonism. *J Neurol Neurosurg Psychiatry,* 38(8)**,** 787-93.

Ekbom K, Lindholm H & Ljungberg L. 1972. New dystonic syndrome associated with butyrophenone therapy. *Z Neurol,* 202(2)**,** 94-103.

Espay AJ, Li JY, Johnston L, et al. 2005. Mirror movements in parkinsonism: evaluation of a new clinical sign. *J Neurol Neurosurg Psychiatry,* 76(10)**,** 1355-8.

Espay AJ, Morgante F, Gunraj C, et al. 2006. Mirror movements in Parkinson's disease: effect of dopaminergic drugs. *J Neurol Neurosurg Psychiatry,* 77(10)**,** 1194-5.

Farley BG & Koshland GF. 2005. Training BIG to move faster: the application of the speed-amplitude relation as a rehabilitation strategy for people with Parkinson's disease. *Exp Brain Res,* 167(3)**,** 462-7.

Fasano A, Di Matteo A, Vitale C, et al. 2011. Reversible Pisa syndrome in patients with Parkinson's disease on rasagiline therapy. *Mov Disord,* 26(14)**,** 2578-80.

Fasano A, Evoli A, Piano C, et al. 2008. Myasthenia gravis: an unrecognized cause of head drop in Parkinson's disease. *Parkinsonism Relat Disord,* 14(2)**,** 164-5.

Fietzek UM, Schroeteler FE & Ceballos-Baumann AO. 2009. Goal attainment after treatment of parkinsonian camptocormia with botulinum toxin. *Mov Disord,* 24(13)**,** 2027-8.

Flowers JM, Hicklin LA & Marion M-H. 2011. Anterior and posterior sagittal shift in cervical dystonia: A clinical and electromyographic study, including a new EMG approach of the longus colli muscle. *Mov Disord,* 26(13)**,** 2409-2414.

Fox C, Ebersbach G, Ramig L, et al. 2012. LSVT LOUD and LSVT BIG: Behavioral Treatment Programs for Speech and Body Movement in Parkinson Disease. *Parkinsons Dis,* 2012(391946.

Frank MJ, Seeberger LC & O'Reilly RC. 2004. By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science,* 306(5703)**,** 1940-3.

Franzén E, Paquette C, Gurfinkel VS, et al. 2009. Reduced performance in balance, walking and turning tasks is associated with increased neck tone in Parkinson's disease. *Exp Neurol,* 219(2)**,** 430-438.

Fujimoto K. 2006. Dropped head in Parkinson's disease. *J Neurol,* 253 (Suppl 7)**,** VII21-26.

Funabe S, Tanaka R, Hayashi A, et al. 2013. Reversible Dropped Head Syndrome after Hemispheric Striatal Infarction. *J Stroke Cerebrovasc Dis***,** 10.1016/j.jstrokecerebrovasdis.2013.05.017.

Furusawa Y, Mukai Y, Kawazoe T, et al. 2012a. Long-term effect of repeated lidocaine injections into the external oblique for upper camptocormia in Parkinson's disease. *Parkinsonism Relat Disord,* 19(3)**,** 350-4.

Furusawa Y, Mukai Y, Kobayashi Y, et al. 2012b. Role of the external oblique muscle in upper camptocormia for patients with Parkinson's disease. *Mov Disord,* 27(6)**,** 802-3.

Gdynia HJ, Sperfeld AD, Unrath A, et al. 2009. Histopathological analysis of skeletal muscle in patients with Parkinson's disease and 'dropped head'/'bent spine' syndrome. *Parkinsonism Relat Disord,* 15(9)**,** 633-9.

Gerton BK, Theeler B & Samii A. 2010. Backpack treatment for camptocormia. *Mov Disord,* 25(2)**,** 247-8.

Gibb WR & Lees AJ. 1989. The significance of the Lewy body in the diagnosis of idiopathic Parkinson's disease. *Neuropathol Appl Neurobiol,* 15(1)**,** 27-44.

Glass GA, Ku S, Ostrem JL, et al. 2009. Fluoroscopic, EMG-guided injection of botulinum toxin into the longus colli for the treatment of anterocollis. *Parkinsonism Relat Disord,* 15(8)**,** 610-3.

Goetz CG, Tilley BC, Shaftman SR, et al. 2008. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord,* 23(15)**,** 2129-70.

Goldstein L & Waugh T. 1973. Classification and terminology of scoliosis. *Clin Orthop Relat Res,* Jun(93)**,** 10-22.

Goodwin VA, Richards SH, Taylor RS, et al. 2008. The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. *Mov Disord,* 23(5)**,** 631-40.

Grimes JD, Hassan MN, Trent G, et al. 1987. Clinical and radiographic features of scoliosis in Parkinson's disease. *Adv Neurol,* 45(353-5.

Hackney ME & Earhart GM. 2009. Backward walking in Parkinson's disease. *Mov Disord,* 24(2)**,** 218-23.

Hadavi S, Noyce A, Leslie R, et al. 2011. Stiff person syndrome. *Pract Neurol,* 11(5)**,** 272-282.

Hagenacker T, Gerwig M, Gasser T, et al. 2013. Pallidal deep brain stimulation relieves camptocormia in primary dystonia. *J Neurol,* 260(7)**,** 1833-7.

Hardy J. 2010. Genetic Analysis of Pathways to Parkinson Disease. *Neuron,* 68(2)**,** 201-206.

Hayashi R, Aizawa J, Nagase H, et al. 2010. Lateral inclination of the trunk and falling frequency in Parkinson's disease patients. *Electromyogr Clin Neurophysiol,* 50(5)**,** 195-202.

Hellmann MA, Djaldetti R, Israel Z, et al. 2006. Effect of deep brain subthalamic stimulation on camptocormia and postural abnormalities in idiopathic Parkinson's disease. *Mov Disord,* 21(11)**,** 2008-10.

Hemmi S, Kurokawa K, Izawa N, et al. 2011. Dramatic response of dropped head sign to treatment with steroid in Parkinson's disease: report of three cases. *Intern*

*Med,* 50(7)**,** 757-61.

Herrera-Marschitz M, Utsumi H & Ungerstedt U. 1990. Scoliosis in rats with experimentally-induced hemiparkinsonism: dependence upon striatal dopamine denervation. *J Neurol Neurosurg Psychiatry,* 53(1)**,** 39-43.

Herting B, Wunderlich S, Glockler T, et al. 2004. Computed tomographically-controlled injection of botulinum toxin into the longus colli muscle in severe anterocollis. *Mov Disord,* 19(5)**,** 588-90.

Hoehn MM & Yahr MD. 1967. Parkinsonism: onset, progression and mortality. *Neurology,* 17(5)**,** 427-42.

Horak FB, Dimitrova D & Nutt JG. 2005. Direction-specific postural instability in subjects with Parkinson's disease. *Exp Neurol,* 193(2)**,** 504-21.

Hughes AJ, Daniel SE, Kilford L, et al. 1992. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry,* 55(3)**,** 181-4.

Hurst AF. 1918. The Bent Back of Soldiers. *Br Med J,* 2(3023)**,** 621-624 1.

Indo T & Ando K. 1980. [Studies on the scoliosis of Parkinsonism (In Japanese)]. *Rinsho Shinkeigaku,* 20(1)**,** 40-6.

Inzelberg R, Hattori N, Nisipeanu P, et al. 2003. Camptocormia, axial dystonia, and parkinsonism: phenotypic heterogeneity of a parkin mutation. *Neurology,* 60(8)**,** 1393-4.

Jankovic J. 2010. Camptocormia, head drop and other bent spine syndromes: heterogeneous etiology and pathogenesis of parkinsonian deformities. *Mov Disord,* 25(5)**,** 527-8.

Jankovic J, McDermott M, Carter J, et al. 1990. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. *Neurology,* 40(10)**,** 1529-34.

Jorens P, Eycken M, Parizel G, et al. 1989. Antecollis in parkinsonism. *Lancet,* 333(8650)**,** 1320-1321.

Kashihara K & Imamura T. 2012. Clinical correlates of anterior and lateral flexion of the thoracolumbar spine and dropped head in patients with Parkinson's disease. *Parkinsonism Relat Disord,* 18(3)**,** 290-3.

Kashihara K, Ohno M & Tomita S. 2006. Dropped head syndrome in Parkinson's disease. *Mov Disord,* 21(8)**,** 1213-6.

Kataoka H, Tonomura Y, Eura N, et al. 2012. Painful abdominal contractions in patients with Parkinson disease. *J Clin Neurosci,* 19(4)**,** 624-7.

Kataoka H & Ueno S. 2011. Dropped head associated with amantadine in Parkinson disease. *Clin Neuropharmacol,* 34(1)**,** 48-9.

Keijsers NL, Admiraal MA, Cools AR, et al. 2005. Differential progression of proprioceptive and visual information processing deficits in Parkinson's disease. *Eur J Neurosci,* 21(1)**,** 239-48.

Kerr TP, Lin JP, Gresty MA, et al. 2008. Spinal stability is improved by inducing a lumbar lordosis in boys with Duchenne Muscular Dystrophy: a pilot study. *Gait Posture,* 28(1)**,** 108-12.

Khan NL, Graham E, Critchley P, et al. 2003. Parkin disease: a phenotypic study of a large case series. *Brain,* 126(Pt 6)**,** 1279-92.

Koller H, Acosta F, Zenner J, et al. 2010. Spinal surgery in patients with Parkinson's disease: experiences with the challenges posed by sagittal imbalance and the Parkinson's spine. *Eur Spine J,* 19(10)**,** 1785-94.

Konczak J, Krawczewski K, Tuite P, et al. 2007. The perception of passive motion in Parkinson's disease. *J Neurol,* 254(5)**,** 655-63.

Kottlors M, Kress W, Meng G, et al. 2010. Facioscapulohumeral muscular dystrophy presenting with isolated axial myopathy and bent spine syndrome. *Muscle Nerve,* 42(2)**,** 273-5.

Krupp L, LaRocca N, Muir-Nash J, et al. 1989. The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol,* 46(10)**,** 1121-1123.

La Grone MO. 1988. Loss of lumbar lordosis. A complication of spinal fusion for scoliosis. *Orthop Clin North Am,* 19(2)**,** 383-93.

Lafage V, Schwab F, Skalli W, et al. 2008. Standing balance and sagittal plane spinal deformity - Analysis of spinopelvic and gravity line parameters. *Spine,* 33(14)**,** 1572-1578.

Lange D, Fetell M, Lovelace R, et al. 1986. The Floppy Head Syndrome. *Ann Neurol,* 20(1)**,** 133.

Langston JW, Ballard P, Tetrud JW, et al. 1983. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science,* 219(4587)**,** 979-80.

Laroche M & Cintas P. 2010. Bent spine syndrome (camptocormia): A retrospective study of 63 patients. *Joint Bone Spine,* 77(6)**,** 593-596.

Lava NS & Factor SA. 2001. Focal myopathy as a cause of anterocollis in Parkinsonism. *Mov Disord,* 16(4)**,** 754-6.

LeDoux MS & Brady KA. 2003. Secondary cervical dystonia associated with structural lesions of the central nervous system. *Mov Disord,* 18(1)**,** 60-69.

Legaye J, Duval-Beaupere G, Hecquet J, et al. 1998. Pelvic incidence: a fundamental pelvic parameter for three-dimensional regulation of spinal sagittal curves. *Eur Spine J,* 7(2)**,** 99-103.

Lemmers RJ, van der Vliet PJ, Klooster R, et al. 2010. A unifying genetic model for facioscapulohumeral muscular dystrophy. *Science,* 329(5999)**,** 1650-3.

Lepoutre AC, Devos D, Blanchard-Dauphin A, et al. 2006. A specific clinical pattern of camptocormia in Parkinson's disease. *J Neurol Neurosurg Psychiatry,* 77(11)**,** 1229-1234.

Lin H, Nagaoka M, Hayashi Y, et al. 2013. Pathophysiological analysis of dropped head syndrome caused by various diagnoses-Based on surface EMG findings and responses to physiotherapy. *Rinsho Shinkeigaku,* 53(6)**,** 430-8.

Lindsay DC, Freeman JG & Record CO. 1986. Unilateral hyperhidrosis associated with underlying intrathoracic neoplasia. *Thorax,* 41(10)**,** 814-5.

Lyons M, Boucher O, Patel N, et al. 2012. Long-term benefit of bilateral subthalamic deep brain stimulation on camptocormia in Parkinson's disease. *Turk Neurosurg,* 22(4)**,** 489-92.

Malfair D, Flemming A, Dvorak M, et al. 2010. Radiographic Evaluation of Scoliosis: Review. *AJR Am J Roentgenol,* 194(S8-S22.

Mann GE, Finn SM & Taylor PN. 2008. A pilot study to investigate the feasibility of electrical stimulation to assist gait in Parkinson's disease. *Neuromodulation,* 11(2)**,** 143-9.

Margraf NG, Wrede A, Rohr A, et al. 2010. Camptocormia in idiopathic Parkinson's disease: a focal myopathy of the paravertebral muscles. *Mov Disord,* 25(5)**,** 542-51.

Martin JP. 1965a. Curvature of the spine in post-encephalitic parkinsonism. *J Neurol Neurosurg Psychiatry,* 28(5)**,** 395-400.

Martin JP. 1965b. The globus pallidus in post-encephalitic parkinsonism. *J Neurol Sci,* 2(4)**,** 344-65.

Martin JP. 1965c. Tilting reactions and disorders of the basal ganglia. *Brain,* 88(5)**,** 855-874.

Martin JP 1967. *The Basal Ganglia and Posture,* London, Pitman Medical Publishing.

McQuain MT, Sinaki M, Shibley LD, et al. 1993. Effect of electrical stimulation on lumbar paraspinal muscles. *Spine,* 18(13)**,** 1787-92.

Medical Research Council. 2000. A framework for the development and evaluation of RCTs for complex interventions to improve health. London: MRC.

Merello M, Nouzeilles MI, Arce GP, et al. 2002. Accuracy of acute levodopa challenge for clinical prediction of sustained long-term levodopa response as a major criterion for idiopathic Parkinson's disease diagnosis. *Mov Disord,* 17(4)**,** 795-798.

Meyerding H. 1931. Spondylolisthesis. *J Bone and Joint Surg,* 13(39-48.

Micheli F, Cersosimo MG & Piedimonte F. 2005. Camptocormia in a patient with Parkinson disease: beneficial effects of pallidal deep brain stimulation. Case report. *J Neurosurg,* 103(6)**,** 1081-3.

Nash CL & Moe JH. 1969. A study of vertebral rotation. *J Bone Joint Surg Am* 51(2)**,** 223-9.

Nasreddine ZS, Phillips NA, Bédirian V, et al. 2005. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *J Am Geriatr Soc,* 53(4)**,** 695-699.

Negrini A, Parzini S, Negrini M, et al. 2008. Adult scoliosis can be reduced through specific SEAS exercises: a case report. *Scoliosis,* 3(20-20.

Nieves AV, Miyasaki JM & Lang AE. 2001. Acute onset dystonic camptocormia caused by lenticular lesions. *Mov Disord,* 16(1)**,** 177-80.

Nikfekr E, Kerr K, Attfield S, et al. 2002. Trunk movement in Parkinson's disease during rising from seated position. *Mov Disord,* 17(2)**,** 274-82.

Nova IC, Perracini MR & Ferraz HB. 2004. Levodopa effect upon functional balance of Parkinson's disease patients. *Parkinsonism Relat Disord,* 10(7)**,** 411-415.

Nussbaum RL & Ellis CE. 2003. Alzheimer's disease and Parkinson's disease. *N Engl J Med,* 348(14)**,** 1356-64.

O'Brien M, Kuklo T, Blanke K, et al. 2004. *Radiographic Measurements Manual: Spinal Deformity Study Group (SDSG),* USA, Metronic Sofamor Danek.

O'Riordan S PA, Liu X, Aziz TZ, Nandi D, Bain PG. 2009. Camptocormia - response to bilateral globus pallidus interna stimulation in three patients. *Mov Disord,* 24(Suppl 1)**,** 489.

O'Sullivan JD, Said CM, Dillon LC, et al. 1998. Gait analysis in patients with Parkinson's disease and motor fluctuations: Influence of levodopa and comparison with other measures of motor function. *Mov Disord,* 13(6)**,** 900-906.

Oliveira A, Massano J & Rosas MJ. 2012. Dropped head syndrome in early-onset Parkinson disease treated with bilateral subthalamic stimulation: clinical, imaging, EMG, and biopsy findings. *Neurol Sci,* 34(4)**,** 593-4.

Onuaguluchi G. 1964. Deformities in Parkinsonism. *Parkinsonism.* Butterworth: London.

Padberg GW, Lunt PW, Koch M, et al. 1991. Diagnostic criteria for facioscapulohumeral muscular dystrophy. *Neuromuscul Disord,* 1(4)**,** 231-4.

Pahapill PA & Lozano AM. 2000. The pedunculopontine nucleus and Parkinson's disease. *Brain,* 123 (Pt 9)**,** 1767-83.

Papapetropoulos S, Baez S, Zitser J, et al. 2008. Retrocollis: classification, clinical phenotype, treatment outcomes and risk factors. *Eur Neurol,* 59(1-2)**,** 71-5.

Parkinson J. 1817. *An Essay on the Shaking Palsy,* London, Whittington and Rowland.

Pastor MA, Day BL & Marsden CD. 1993. Vestibular induced postural responses in Parkinson's disease. *Brain,* 116 (Pt 5)**,** 1177-90.

Peek AC, Quinn N, Casey AT, et al. 2009. Thoracolumbar spinal fixation for camptocormia in Parkinson's disease. *J Neurol Neurosurg Psychiatry,* 80(11)**,** 1275-8.

Pereira EAC, Wilson-MacDonald J, Green AL, et al. 2010. Posterior occipitocervical instrumented fusion for dropped head syndrome after deep brain stimulation. *Journal of Clinical Neuroscience,* 17(4)**,** 541-542.

Perennou D, Marcelli C, Herisson C, et al. 1994. Epidemiologic Aspects in a Low-Back Pain Population. *Spine,* 19(2)**,** 123-128.

Peto V, Jenkinson C, Fitzpatrick R, et al. 1995. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Qual Life Res,* 4(3)**,** 241-8.

Pollak L, Prohorov T, Kushnir M, et al. 2009. Vestibulocervical reflexes in idiopathic Parkinson disease. *Neurophysiol Clin,* 39(4-5)**,** 235-40.

Proctor F, Riklan M, Cooper I, et al. 1964. Judgment of visual and postural vertical by Parkinsonian patients. *Neurology,* 14(287-93.

Quinn N. 1989. Disproportionate antecollis in Multiple System Atrophy. *Lancet,* 333(8642)**,** 844.

Rascol O, Sabatini U, Fabre N, et al. 1995. Abnormal vestibuloocular reflex cancellation in multiple system atrophy and progressive supranuclear palsy but not in Parkinson's disease. *Mov Disord,* 10(2)**,** 163-70.

Richer P & Meige H. 1895. Etude morphologique sur la Maladiede Parkinson. *Nouvelle Iconographie de la Salpetriere,* 8, 361-71.

Roussouly P & Pinheiro-Franco J. 2011. Biomechanical analysis of the spino-pelvic organization and adaptation in pathology. *Eur Spine J,* 20 (Suppl 5)**,** 609-18.

Sailer A, Molnar GF, Paradiso G, et al. 2003. Short and long latency afferent inhibition in Parkinson's disease. *Brain,* 126(Pt 8)**,** 1883-94.

Sako W, Nishio M, Maruo T, et al. 2009. Subthalamic nucleus deep brain stimulation for camptocormia associated with Parkinson's disease. *Mov Disord,* 24(7)**,** 1076-9.

Salazar Z, Tschopp L, Calandra C, et al. 2008. Pisa syndrome and parkinsonism secondary to valproic acid in Huntington's disease. *Mov Disord,* 23(16)**,** 2430-1.

Savica R, Kumar N, Ahlskog JE, et al. 2012. Parkinsonism and dropped head: dystonia, myopathy or both? *Parkinsonism Relat Disord,* 18(1)**,** 30-4.

Schabitz WR, Glatz K, Schuhan C, et al. 2003. Severe forward flexion of the trunk in Parkinson's disease: focal myopathy of the paraspinal muscles mimicking camptocormia. *Mov Disord,* 18(4)**,** 408-14.

Schenkman ML, Clark K, Xie T, et al. 2001. Spinal movement and performance of a standing reach task in participants with and without Parkinson disease. *Phys Ther,* 81(8)**,** 1400-11.

Schneider SA, Lang AE, Moro E, et al. 2010. Characteristic head drops and axial extension in advanced chorea-acanthocytosis. *Mov Disord,* 25(10)**,** 1487-91.

Schrag A, Jahanshahi M & Quinn N. 2000. What contributes to quality of life in patients with Parkinson's disease? *J Neurol Neurosurg Psychiatry,* 69(3)**,** 308-12.

Schroeteler FE, Fietzek UM, Ziegler K, et al. 2011. Upright posture in parkinsonian camptocormia using a high-frame walker with forearm support. *Mov Disord,* 26(8)**,** 1560-1.

Schwab FJ, Smith VA, Biserni M, et al. 2002. Adult scoliosis: a quantitative radiographic and clinical analysis. *Spine (Phila Pa 1976),* 27(4)**,** 387-92.

Scoliosis Research Society. 2013. SRS etextbook. www.srs.org

Seiss E, Praamstra P, Hesse CW, et al. 2003. Proprioceptive sensory function in Parkinson's disease and Huntington's disease: evidence from proprioception-related EEG potentials. *Exp Brain Res,* 148(3)**,** 308-19.

Seki M, Takahashi K, Koto A, et al. 2011. Camptocormia in Japanese patients with Parkinson's disease: a multicenter study. *Mov Disord,* 26(14)**,** 2567-71.

Serratrice G & Schiano A. 1976. Scoliose chez les malades parkinsoniens *Nouv Presse Med,* 5(29)**,** 1834.

Sicard J & Alquier L. 1905. Les deviations de la colonne vertebrale dans la maladie de parkinson. *Nouvelle Iconographie de la Salpetriere,* 16, 377-384.

Siewe J, Zarghooni K, Rollinghoff M, et al. 2013. [Complication Analysis of Spinal Interventions in Adult Central Movement Disorders and Scoliosis.]. *Z Orthop Unfall***,** 10.1055/s-0032-1328664.

Spampinato U, Debruxelles S, Rouanet M, et al. 2013. Head drops are also observed in advanced Huntington disease. *Parkinsonism Relat Disord,* 19(5)**,** 569-70.

Spanaki C, Zafeiris S & Plaitakis A. 2010. Levodopa-aggravated lateral flexion of the neck and trunk as a delayed phenomenon of unilateral pallidotomy. *Mov Disord,* 25(5)**,** 655-6.

Spuler S, Krug H, Klein C, et al. 2010. Myopathy causing camptocormia in idiopathic Parkinson's disease: a multidisciplinary approach. *Mov Disord,* 25(5)**,** 552-9.

Stebbins GT, Goetz CG, Burn DJ, et al. 2013. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. *Mov Disord,* 28(5)**,** 668-70.

Strafella AP, Lozano AM, Ballanger B, et al. 2008. rCBF changes associated with PPN stimulation in a patient with Parkinson's disease: a PET study. *Mov Disord,* 23(7)**,** 1051-4.

Sutter P, Forster T & Kulling F. 2012. [Spinal deformity in Parkinson's disease : A treatment proposal.]. *Der Unfallchirurg***,** 10.1007/s00113-012-2271-3.

Suzuki M, Hirai T, Ito Y, et al. 2008. Pramipexole-induced antecollis in Parkinson's disease. *J Neurol Sci,* 264(1-2)**,** 195-7.

Suzuki T & Matsuzaka H. 2002. Drug-induced Pisa syndrome (pleurothotonus): epidemiology and management. *CNS Drugs,* 16(3)**,** 165-74.

Tabamo RE, Fernandez HH, Friedman JH, et al. 2000. Spinal surgery for severe scoliosis in Parkinson's disease. *Med Health R I,* 83(4)**,** 114-5.

Taguchi Y, Takashima S & Tanaka K. 2008. Pramipexole-induced dropped head syndrome in Parkinson's disease. *Intern Med,* 47(22)**,** 2011-2.

Tassorelli C, Furnari A, Buscone S, et al. 2012. Pisa syndrome in Parkinson's disease: clinical, electromyographic, and radiological characterization. *Mov Disord,* 27(2)**,** 227-35.

Thani NB, Bala A, Kimber TE, et al. 2011. High-frequency pallidal stimulation for camptocormia in Parkinson disease: case report. *Neurosurgery,* 68(5)**,** E1501-5.

Tiller J, Stygar MK, Hess C, et al. 1982. Treatment of functional chronic stooped posture using a training device and behavior therapy. A case report. *Phys Ther,* 62(11)**,** 1597-600.

Tinazzi M, Juergenson I, Squintani G, et al. 2013. Pisa syndrome in Parkinson’s

disease: an electrophysiological and imaging study. *J Neurol*, 10.1007/s00415-013-6945-8.

Tiple D, Fabbrini G, Colosimo C, et al. 2009. Camptocormia in Parkinson disease: an epidemiological and clinical study. *J Neurol Neurosurg Psychiatry,* 80(2), 145-8.

Tomlinson CL, Stowe R, Patel S, et al. 2010. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord,* 25(15), 2649-2653.

Uitti RJ, Baba Y, Whaley NR, et al. 2005. Parkinson disease: handedness predicts asymmetry. *Neurology,* 64(11), 1925-30.

Umapathi T, Chaudhry V, Cornblath D, et al. 2002. Head drop and camptocormia. *J Neurol Neurosurg Psychiatry,* 73(1), 1-7.

Umemura A, Oka Y, Ohkita K, et al. 2009. Effect of subthalamic deep brain stimulation on postural abnormality in Parkinson disease. *J Neurosurg,* 112(6), 1283-8.

Unal-Cevik I & Temucin CM. 2009. Head drop in an elder Parkinson's disease after development of myasthenia gravis. *Mov Disord,* 24(13), 2025-6.

Ungerstedt U, Butcher LL, Butcher SG, et al. 1969. Direct chemical stimulation of dopaminergic mechanisms in the neostriatum of the rat. *Brain Res,* 14(2), 461-71.

Upadhyaya CD, Starr PA & Mummaneni PV. 2010. Spinal deformity and Parkinson disease: a treatment algorithm. *Neurosurg Focus,* 28(3), E5.

Uzawa A, Mori M, Kojima S, et al. 2009. Dopamine agonist-induced antecollis in Parkinson's disease. *Mov Disord,* 24(16), 2408-11.

van de Warrenburg BP, Bhatia KP & Quinn NP. 2007a. Pisa syndrome after unilateral pallidotomy in Parkinson's disease: an unrecognised, delayed adverse event? *J Neurol Neurosurg Psychiatry,* 78(3), 329-30.

van de Warrenburg BP, Cordivari C, Ryan AM, et al. 2007b. The phenomenon of disproportionate antecollis in Parkinson's disease and multiple system atrophy. *Mov Disord,* 22(16), 2325-31.

van der Maarel S, Frants R & Padberg G. 2007. Facioscapulohumeral muscular dystrophy. *Biochim Biophys Acta,* 1772(2), 186-94.

Vanacore N, Suzzareddu G, Maggini M, et al. 2005. Pisa syndrome in a cohort of Alzheimer's disease patients. *Acta Neurol Scand,* 111(3), 199-201.

Vaugoyeau M & Azulay JP. 2010. Role of sensory information in the control of postural orientation in Parkinson's disease. *J Neurol Sci,* 289(1-2), 66-8.

Vaugoyeau M, Hakam H & Azulay J. 2011. Proprioceptive impairment and postural

orientation control in Parkinson's Disease. *Hum Mov Sci,* 30(2)**,** 405-14.

Vaugoyeau M, Viallet F, Aurenty R, et al. 2006. Axial rotation in Parkinson's disease. *J Neurol Neurosurg Psychiatry,* 77(7)**,** 815-821.

Vaugoyeau M, Viel S, Amblard B, et al. 2008. Proprioceptive contribution of postural control as assessed from very slow oscillations of the support in healthy humans. *Gait Posture,* 27(2)**,** 294-302.

Vaugoyeau M, Viel S, Assaiante C, et al. 2007. Impaired vertical postural control and proprioceptive integration deficits in Parkinson's disease. *Neuroscience,* 146(2)**,** 852-63.

Villarejo A, Camacho A, Garcia-Ramos R, et al. 2003. Cholinergic-dopaminergic imbalance in Pisa syndrome. *Clin Neuropharmacol,* 26(3)**,** 119-21.

Vitale C, Marcelli V, Furia T, et al. 2011. Vestibular impairment and adaptive postural imbalance in parkinsonian patients with lateral trunk flexion. *Mov Disord,* 26(8)**,** 1458-63.

Von Coelln R, Raible A, Gasser T, et al. 2008. Ultrasound-guided injection of the iliopsoas muscle with botulinum toxin in camptocormia. *Mov Disord,* 23(6)**,** 889-892.

Vrtovec T, Pernus F & Likar B. 2009a. A review of methods for quantitative evaluation of axial vertebral rotation. *Eur Spine J,* 18(8)**,** 1079-90.

Vrtovec T, Pernus F & Likar B. 2009b. A review of methods for quantitative evaluation of spinal curvature. *Eur Spine J,* 18(5)**,** 593-607.

Wadia PM, Tan G, Munhoz RP, et al. 2011. Surgical correction of kyphosis in patients with camptocormia due to Parkinson's disease: a retrospective evaluation. *J Neurol Neurosurg Psychiatry,* 82(4)**,** 364-8.

Wang YT, Singh D & Poh SC. 1981. Hemihyperhidrosis and intrathoracic malignancy. *Singapore Med J,* 22(2)**,** 86-8.

Wood-Allum C, Brennan P, Hewitt M, et al. 2004. Clinical and histopathological heterogeneity in patients with 4q35 facioscapulohumeral muscular dystrophy (FSHD). *Neuropathol Appl Neurobiol,* 30(2)**,** 188-91.

World Health Organization. 1998. Well-Being measures in primary health care: The DepCare Project. Consensus meeting, Stockholm.

Wrede A, Margraf NG, Goebel HH, et al. 2012. Myofibrillar disorganization characterizes myopathy of camptocormia in Parkinson's disease. *Acta Neuropathologica,* 123(3)**,** 419-32.

Wright WG, Gurfinkel VS, King LA, et al. 2010. Axial kinesthesia is impaired in Parkinson's disease: effects of levodopa. *Exp Neurol,* 225(1)**,** 202-9.

Wright WG, Gurfinkel VS, Nutt J, et al. 2007. Axial hypertonicity in Parkinson's disease: direct measurements of trunk and hip torque. *Exp Neurol,* 208(1)**,** 38-46.

Wunderlich S, Csoti I, Reiners K, et al. 2002. Camptocormia in Parkinson's disease mimicked by focal myositis of the paraspinal muscles. *Mov Disord,* 17(3)**,** 598-600.

Yamada H, Katayama Y & Yamamoto T. 2003. Parkinson's disease and dropped head. *Rinsho Shinkeigaku,* 43(955.

Yamada K, Goto S, Matsuzaki K, et al. 2006. Alleviation of camptocormia by bilateral subthalamic nucleus stimulation in a patient with Parkinson's disease. *Parkinsonism Relat Disord,* 12(6)**,** 372-5.

Yang YR, Yen JG, Wang RY, et al. 2005. Gait outcomes after additional backward walking training in patients with stroke: a randomized controlled trial. *Clin Rehabil,* 19(3)**,** 264-73.

Yokochi F. 2006. Lateral flexion in Parkinson's disease and Pisa syndrome. *J Neurol,* 253 (Suppl 7)**,** VII17-20.

Yoshiyama Y, Takama J & Hattori T. 1999. The dropped head sign in parkinsonism. *J Neurol Sci,* 167(1)**,** 22-5.

Zarate-Kalfopulos B, Romero-Vargas S, Otero-Camara E, et al. 2012. Differences in pelvic parameters among Mexican, Caucasian, and Asian populations. *J Neurosurg Spine,* 16(5)**,** 516-9.

Zetterberg C, Hansson T, Lindstrom J, et al. 1983. Postural and time-dependent effects on body height and scoliosis angle in adolescent idiopathic scoliosis. *Acta Orthop Scand,* 54(6)**,** 836-40.