Predictors and Pathophysiology of Axial Postural Abnormalities in Parkinsonism: A Scoping Review.

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Movement Disorders
CLINICAL PRACTICE

REVIEW

Predictors and Pathophysiology of Axial Postural Abnormalities in Parkinsonism: A Scoping Review

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Abstract: Background: Postural abnormalities involving the trunk are referred to as axial postural abnormalities and can be observed in over 20% of patients with Parkinson's disease (PD) and in atypical parkinsonism. These symptoms are highly disabling and frequently associated with back pain and a worse quality of life in PD. Despite their frequency, little is known about the pathophysiology of these symptoms and scant data are reported about their clinical predictors, making it difficult to prompt prevention strategies.

Objectives: We conducted a scoping literature review of clinical predictors and pathophysiology of axial postural abnormalities in patients with parkinsonism to identify key concepts, theories and evidence on this topic.

Methods: We applied a systematic approach to identify studies, appraise quality of evidence, summarize main findings, and highlight knowledge gaps.

Results: Ninety-two articles were reviewed: 25% reported on clinical predictors and 75% on pathophysiology. Most studies identified advanced disease stage and greater motor symptoms severity as independent clinical

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predictors in both PD and multiple system atrophy. Discrepant pathophysiology data suggested different potential central and peripheral pathogenic mechanisms.
Conclusions: The recognition of clinical predictors and pathophysiology of axial postural abnormalities in parkinsonism is far from being elucidated due to literature bias, encompassing different inclusion criteria and measurement tools and heterogeneity of patient samples. Most studies identified advanced disease stage and higher burden of motor symptoms as possible clinical predictors. Pathophysiology data point toward many different (possibly non-mutually exclusive) mechanisms, including dystonia, rigidity, proprioceptive and vestibular impairment, and higher cognitive deficits.

Postural abnormalities involving the trunk are referred to as axial postural abnormalities and can be observed in over 20% of patients with Parkinson's disease (PD) during the disease course.[1] Similarly, patients with other forms of parkinsonism, including multiple system atrophy (MSA), Lewy body dementia (DLB), supranuclear gaze palsy (PSP), can present axial postural abnormalities, with even higher prevalence, especially in MSA (up to 67%).[2,3] Axial postural abnormalities are part of the group of axial symptoms affecting parkinsonian patients and consist of abnormal trunk or neck flexion in the upright position, often worsened by prolonged standing or walking.[1,2,4,5] These symptoms proved to be highly disabling for patients, and associated with more back pain, increased risk of falling and a worse quality of life.[2,5,6] Noteworthy, axial postural abnormalities can be also observed as an idiopathic entity in people without parkinsonism or other known neurological diseases, with some forms like mild–moderate anterior trunk flexion being more common in the elderly population.[7]

Recently, an expert-based consensus was reached for the harmonization of nosology and cut-off values to define and categorize axial postural abnormalities in PD patients[1,4]; accordingly, camptocormia was defined as an involuntary anterior trunk flexion with thoracic fulcrum >45° or lumbar fulcrum >30°, Pisa syndrome as an involuntary lateral trunk flexion >10°, and antecollis as an involuntary anterior neck flexion >45°. The terms "anterior trunk flexion," with thoracic (≥25° to ≤45°) or lumbar fulcrum (>15° to ≤30°), "lateral trunk flexion" (≥5° to ≤10°), and "anterior neck flexion" (>35° to ≤45°) were chosen for milder postural abnormalities.[1,4]

Despite its frequency and the relevant impact on patients' quality of life, there is only little evidence about prevention and management of axial postural abnormalities. The difficulty of developing prevention and management strategies can be due to the scant knowledge about pathophysiology of these symptoms and scarce data about their clinical predictors. As most axial motor symptoms, axial postural abnormalities are typically no or poorly responsive to dopaminergic therapies.[2] No other specific treatment has been found to manage these symptoms, with the exception of physiotherapy, which proved to be helpful for the improvement of camptocormia[8,9] and Pisa syndrome[10,11] although its efficacy in the long term is currently not sustained by strong literature evidence.[2] Thus, recommendations for management and prevention of these disabling symptoms remain an unmet need.[4] The possibility to identify adequate strategies for treatment and prevention would be increased by a better knowledge on the underlying pathophysiological mechanisms and on the clinical predictors (or risk factors) for their development. To pursue the aim of identifying key concepts, examining emerging evidence, and highlighting knowledge gaps on this topic, we conducted a scoping literature review of clinical predictors and pathophysiology of axial postural abnormalities in patients with parkinsonism.

Methods

Protocol

We performed a scoping review according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension.[12–14] Given the limited scientific evidence on this topic, the interest on both clinical predictors and the broad scope of pathophysiological mechanisms, and the existence of different axial postural abnormalities, along with the high heterogeneity of studies, we opted for a scoping review instead of a traditional systematic review.

Step 1: Identification of Research Questions

The aim of this scoping review was to analyze the number, quality, and bias of studies investigating clinical predictors and pathophysiology of axial postural abnormalities in patients with PD, to identify current knowledge gaps, and to present a roadmap for future studies.

Step 2: Identification of Studies

Information Sources

We searched the electronic databases PubMed, OVID Medline, Scopus, and Google Scholar from their inception to June 2022. The search terms were MeSH terms for movement disorders and the main forms of parkinsonism: Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, dementia, Lewy body, parkinsonian disorders, corticobasal syndrome. The keywords for axial postural abnormalities were: Pisa syndrome, camptocormia, cervical dystonia, retrocollis, and anterocollis/antecollis.

Other terms were: postural syndrome, spinal curvatures, stooped posture, anterior trunk flexion, forward trunk flexion, lateral trunk flexion, and axial manifestation. The full electronic search strategy is presented in the Supplementary Material in Data S1.

Eligibility Criteria

Studies were included if they reported data on clinical predictors and/or pathophysiology of axial postural abnormalities in patients with PD or atypical Parkinsonism, encompassing MSA, dementia with Lewy Bodies (DLB), PSP, and corticobasal syndrome. Studies reporting drug-induced axial postural abnormalities (ie, stooped posture, camptocormia, anterocollis, Pisa syndrome) were also included. Only studies referring to human subjects and published in English were considered. No restrictions were applied to patient sex, age, ethnicity, disease duration or severity. We excluded systematic and narrative reviews, case report/single case studies, conference abstracts, commentaries, and letters to the editor. Also excluded were studies involving patients with non-degenerative causes of Parkinsonism like normal pressure hydrocephalus, vascular parkinsonism, and drug-induced parkinsonism.[15] The reference list of each record was searched to screen for additional studies not captured by the original search strategy.

Step 3: Study Selection

The records were processed with systematic review management software (Covidence, https://www.covidence.org); duplicate records were eliminated. Six reviewers (D.G., M.D., D.S., C.G., Y.L., C.A.) independently and in pairs screened titles and abstracts by inclusion and exclusion criteria. A third reviewer (V.L., R.W., M.S., M.A-W., J.N., C.A.A.) was called to solve uncertainties and disagreements until consensus was reached. The full text of titles and abstracts was obtained and reviewed.

Step 4: Charting the Data

All authors reported in Step 3 worked in pairs to extract the data. The second person in the pair verified the extracted information. Data were collected and tabulated on an extraction form.

Step 5: Collating, Summarizing, and Reporting Results

We summarized the extracted data and applied qualitative and quantitative descriptive methods to obtain information on: first author, year of publication, study design, number of patients, age, diagnosis, disease stage, type of axial postural abnormality, prevalence, main pathophysiological assessment, clinical predictors, main finding, main study limitations, and quality appraisal. Two investigators independently performed the quality appraisal of each study, which was rated "good", "fair", or "poor" as per the National Heart, Lung, and Blood Institute tools (Research Triangle Institute International. National Heart, Lung, and Blood Institute Quality Appraisal Tools, in accordance with Cochrane handbook recommendations).

Moreover, the full text of all included articles was evaluated for the level of evidence of the results. Evidence levels were attributed as follows, according to the Oxford Centre for Evidence-Based Medicine (CEBM) criteria: (1) RCTs, prospective, homogeneity of results, interventional; (2) Cohort studies with acceptable quality, number of probands and controls adequate to hypothesis, and reasonable homogeneity of results; (3) Case–control or low-quality cohort study; (4) Case report, cross-sectional study; (5) Expert opinion (https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009).

Results

Included and Excluded Studies

Of the total of 4735 records screened, 1964 were excluded because of duplicates and 2405 because they were irrelevant to the topic of this study. A total of 92 records were selected for qualitative data synthesis. Figure 1 illustrates the literature search and the study selection. Of the 92 records, 23 (25%) studies dealt with clinical predictors and 69 (75%) with pathophysiology of axial postural abnormalities in parkinsonism (Supplementary Tables S1 and S2).

Clinical Predictors: Main Findings

The majority of studies on clinical predictors of axial postural abnormalities in parkinsonism involved cohorts of PD patients (21 studies)[1,5,16–34] or MSA patients (two studies).[35,36] The total number of PD patients was 11,609 and the total number of MSA patients was 1448. Overall, camptocormia (or mild forms) was present in 973 patients, Pisa syndrome (or mild forms) in 462, antecollis (or mild forms) in 149, and retrocollis in 21. The study designs were various: 14 were observational cross-sectional studies,[1,5,16,19,23–26,29,30,33–36] one study was retrospective,[17] three studies were prospective,[18,21,31] four were case–control,[20,22,27,28] and one was case series.[32]

The clinical predictors for axial postural abnormalities varied and in the analyses were either unadjusted or adjusted for confounding variables (Supplementary Table S1). Many studies shared the criteria of advanced stage of disease and greater symptom severity (ie, high UPDRS part III score) as independent clinical predictors for the development of axial postural abnormalities in PD and MSA (Supplementary Table S1). Other clinical, less frequently reported predictors (adjusted and unadjusted for potential confounding variables) were male gender, older age, older age at PD onset, longer disease duration, higher doses of levodopa equivalent daily dose and dopamine agonists, history of falls, back pain, and comorbid orthopedic spinal lesions, as well as a higher score of axial symptoms and a higher probability of having an akinetic-rigid phenotype. Also, the presence of motor fluctuations was reported as a potential predictor of axial postural abnormalities in two studies, which not survived to

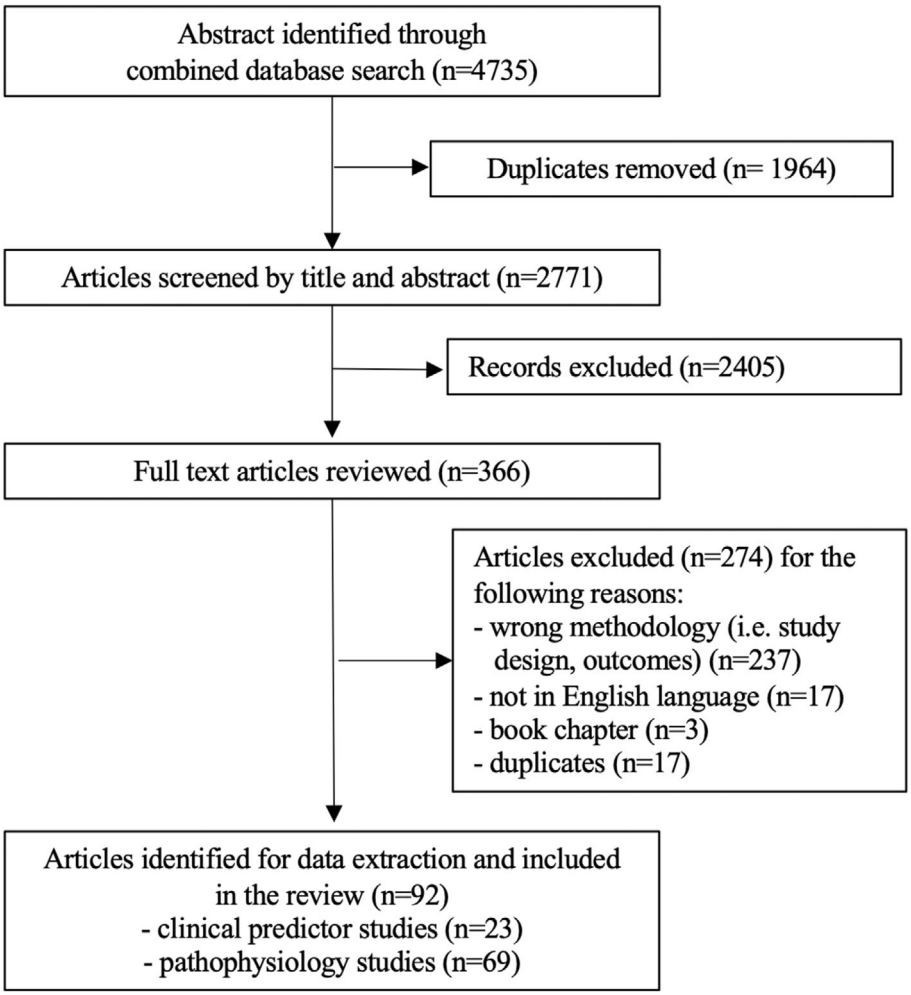

Figure 1. Study flow chart: phases of the scoping review.

analyses including confounders. The major limitations were pitfalls in study design, small sample size, diverse diagnostic criteria to define axial postural abnormalities, and variety of measurement methods. A goniometer, wall goniometer, smartphone, or photographs were used in 14 studies,[1,5,18–21,25–28,30,33,34,36] software-based measurement using Kinovea® in one study,[16] and the Cobb angle in one study.[23] Seven studies reported no use of instruments, tools, or bony reference points in the evaluation of axial postural abnormalities.[17,22,24,29,31,32,35] The score of quality appraisal was good in 43% (n = 10), fair in 35% (n = 8), and poor in 22% (n = 5) of studies (Supplementary Table S1).

The majority of studies regarding clinical predictors have a low level of evidence (class 4: 19 studies), two studies were categorized as class 3b, and two studies as class 2b.

Pathophysiology: Main Findings

The majority of studies on the pathophysiology of axial postural abnormalities in parkinsonism involved cohorts of PD patients (n = 63 studies)[37–99] or a cohort of patients with MSA (n = 1 study)[100] and mixed populations including PD, MSA, PSP, DLB (n = 5 studies).[101–105] The total number of patients was 2181 for PD, 29 for MSA, and 34 for other mixed sample populations. Camptocormia (or mild forms of anterior trunk flexion) was present in 801 patients, Pisa syndrome (or mild forms of lateral trunk flexion) in 666, and antecollis (or mild forms of anterior neck flexion) in 114. There was a wide range of study designs (in some cases more than one study design): 14 were observational cross-sectional, 12 were retrospective, four were prospective, 22 were case–control, one study was a controlled-intervention, 10 were case series, and six had a before-after design.

The pathophysiological mechanisms were explained by a central hypothesis (i.e. imbalance in basal ganglia functioning leading to dystonia/rigidity, altered sensory-motor integration, higher cognitive function deficits) and a peripheral hypothesis (ie, alteration of the musculoskeletal system).

The main study limitations were pitfalls in study design, small sample size, different diagnostic criteria to define axial postural

abnormalities, and use of one or more different measurement methods: standard goniometric measurement with a wall goniometer, smartphone, protractor, inclinometer or photographs was used in 22 studies,[40,47,48,50,51,57,58,60–66,72,73,77,78,81,82,98,101] software-based measurement with NeuroPostureApp, Kinovea, MB Ruler® software, or Image J was used in 12,[37–39,41,44–46,49,51,52,56,97,99] Cobb angle, X-ray in nine,[42,43,55,71,79,81,83–85] a spinal mouse electronic measuring device in one study[91]; 26 studies reported no instrument, tool or bony reference points for evaluating axial postural abnormalities.[53,54,59,67–70,74–76,80,86–90,92–96,100,102–105] The quality appraisal was good in 29% (n = 20), fair in 43% (n = 30), and poor in 28% (n = 19) studies. Various pathophysiological mechanisms and study methodologies were described (Supplementary Table S2).

The majority of studies regarding pathophysiology have a low level of evidence (class 4: 42 studies), 21 studies were categorized as class 3b, five studies as class 2b, and 1 study as class 1b.

Clinical Predictors

Our interpretation of the literature on clinical predictors was complicated by the heterogeneity of the studies and, in general, by the low quality of the evidence. The studies analyzed diverse relationships, associations, risk factors or correlations between clinical variables; however, the study aim (eg, prediction of an outcome or identification of causal mechanisms), was often not clearly stated. The study design sometimes did not match the stated aim or the data analysis failed to predict the outcome or to demonstrate the causal effect. While the majority of studies involved persons with PD, the patient sample was heterogeneous for disease severity and stage, ranging from 2 to 5 on the Hoehn & Yahr scale. Surprisingly, some studies did not even report the disease stage.

One possible issue identified in the literature is that many studies focused on a general presence of axial postural abnormality involving the trunk or neck. Since it is not clear whether abnormal anterior trunk flexion, lateral trunk flexion or anterior neck flexion share the same pathophysiological mechanisms, the search for clinical predictors (other than of their pathophysiological underpinnings) should be better analyzed separately for any form of axial postural abnormality. Moreover, the diagnostic criteria and especially the threshold of trunk flexion degrees for defining an axial postural abnormality (and thus the inclusion in the study as a patient with a postural abnormality) differed across studies and were not stated in many cases. Also, the variability in the tools and the reference bone points for measuring axial postural abnormalities adds further variability. All the above-reported aspects render it difficult to draw robust conclusions from the current literature and represent a possible relevant bias, which could also explain the high variability in frequency of axial postural abnormalities across studies.

Despite the literature limitations, some findings appear to be robustly represented in most studies. Specifically, the findings converge on an advanced stage of disease and greater motor symptom severity as clinical predictors for axial postural abnormalities. The relationship between these associations is unclear: while the mechanisms correlated with the development of axial symptoms are typical of advanced disease stages and thus are associated with more severe motor symptoms, severe axial postural abnormalities (eg, Pisa syndrome and camptocormia) highly affect the motor burden of patients, leading to higher scores of UPDRS. More prospective longitudinal studies are needed not only to confirm these associations but also to elucidate the causal factors for the development of axial postural abnormalities.

Pathophysiology

Several different pathophysiological mechanisms have been hypothesized in patients with axial postural abnormalities. Central mechanisms (ie, imbalance in basal ganglia functioning, higher cognitive function deficits, altered sensory-motor integration, proprioception, vestibular information) and peripheral processes (ie, alteration of the musculoskeletal system) have been investigated. Additional clues to the pathophysiology of axial postural abnormalities are given by small sample size studies suggesting their reversibility after deep-brain stimulation, repetitive trans-spinal magnetic stimulation, unilateral pallidotomy, and after withdrawal of pharmacological therapies.

The key concepts related to the pathophysiology of axial postural abnormalities can be resumed as the possibly concomitant presence of dystonia, impaired proprioception, deficits of higher cognitive functions and of the vestibular system. While most studies and most experts in the field currently point toward central mechanisms as the prime of the development of axial postural abnormalities in parkinsonism, various studies based on electromyographic findings,[41,45,78,81,86,88,91,94,99,101–105] muscle biopsy,[80,86,88,91,94,102,105] and muscle imaging[43,45,51,60,68,69,76,78,81,86,88,89,91,94,96,100,105] indicate the presence of myopathy in trunk muscles of patients with axial postural abnormalities.

Below we discuss the main theories regarding the pathogenesis of axial postural abnormalities, starting from the findings of the various studies included in this scoping review, always keeping in mind the relevant limitations of the current body of literature disclosed in the Results of this review.

Central Mechanisms

Dystonia

An abnormal trunk muscle hyperactivity proved by electromyographic findings has been consistently observed in patients with axial postural abnormalities.[45,51,57,61,63,73–75,78,81,84,85,92,99,102,103] The hypothesis for dystonic muscle activation as a possible cause of axial postural abnormalities is supported by anecdotal studies suggesting that the abnormalities can be alleviated by sensory tricks in some cases[106] and can be improved by botulinum toxin type-A or lidocaine administration—as described for both camptocormia[73,82] and Pisa syndrome.[51] However, these hypotheses

have attracted criticism related to contradictory electromyographic findings between studies and absence of clinical characteristics of dystonia (ie, overflow, twisting movements, sensory trick for Pisa syndrome).[25] In patients with Pisa syndrome, electromyography findings have been inconsistent concerning the side of hyperactivity of paraspinal and non-paraspinal muscles. Some studies demonstrated hyperactivity of paraspinal muscles ipsilateral to the leaning side, whereas others found continuous activity contralateral to the leaning side.[57,61,63,74,81,84,85] However, definitive evidence for a possible dystonic origin of the Pisa syndrome is lacking. Botulinum toxin administered to the paraspinal muscles contralateral to the flexion side was reported efficacious in improving flexion and pain in some patients (though this would not be expected from a mechanical perspective),[51] suggesting that the action of botulinum may extend beyond simple de-contraction of pulling muscles.

In patients with camptocormia with thoracic fulcrum, the bilateral abdominal internal and the external oblique muscles, together with the rectus abdominis muscles may be involved,[45] whereas rectus abdominis and iliopsoas hyperactivity is more frequently observed in patients with camptocormia with lumbar fulcrum.[45,73] The paraspinal muscles (ie, iliocostalis lumborum, longissimus and multifidus) and the rectus femoris to a lesser extent were also found to be hyperactive.[99] Evidence for dystonic activity of non-paraspinal muscles is partially supported by improvement of camptocormia with thoracic fulcrum after injection of lidocaine in the oblique external muscle.[73] However, scientific evidence for clinical benefit is scant and this approach is also very limited in clinical practice.

Antecollis has been suggested to be a clue for MSA, but it also occurs in other parkinsonian conditions, including PD.[102] Neck voluntary movement is limited, but muscle strength appears normal when the residual range of motion is tested during active neck extension.[92,107] Muscle hyperactivity in anterior (sternocleidomastoid muscles and plathysma) and posterior neck muscles (eg, semispinalis, splenius capitis, trapezius, levator scapulae) have been reported.[2,102,103] In most cases, the activation of posterior neck muscles, which are considered "erector spinae" (ie, spine extensors), can be considered compensatory.

Overall, the low number of studies, the lack of objective measures to identify and quantify dystonia, and the difficulties in standardization of needle EMG studies renders dystonia a possible, yet unconfirmed pathogenic mechanisms for axial postural abnormalities in parkinsonism. It is generally recognized that a dystonic phenomenon could be an early and short-lived factor contributing to the development of axial postural abnormalities, while secondary factors such as changes in soft tissue, muscle or spinal cord may develop later in more advanced stages. Further studies are needed to systematically explore the electromyographic patterns of paraspinal and non-paraspinal muscles in very early and in advanced stages of axial postural abnormalities to better understand dystonic pathophysiology and develop tailored pharmacological[108] and non-pharmacological interventions[109] for treatment and prevention.

Rigidity

Few studies to date have suggested in what way rigidity (persistent increase in muscle tone that is not velocity dependent) affects axial muscle tone in patients with PD, and no studies have systematically evaluated rigidity in patients with axial postural abnormalities. Patients with axial postural abnormalities demonstrate in most cases to have a complete or almost complete resolution of trunk or neck flexion when lying on the bed, while when sitting or standing the paravertebral muscles may be highly active.[96,99] Differently from dystonia, parkinsonian rigidity should be consistently present at rest. However, none of the literature studies found in our systematic search used direct measures of axial tone owing to technical difficulties.[110,111]

Impaired Proprioception, Vestibular System and Visuospatial Cognition

Persons with PD have shown an impaired proprioception, and a deficit in proprioception could ensue in poor signal integration while controlling posture.[112,113] Some studies found that patients with camptocormia or Pisa syndrome have a greater velocity of body sway than patients without axial postural abnormalities.[49,72] Clinical observation indicates that patients with camptocormia with a lower fulcrum may have more severe gait and postural control deficits than patients with a thoracic fulcrum or patients without camptocormia.[49] These findings suggest that misalignment of posture can contribute to increased postural instability.

Another pivotal aspect for postural control is the vestibular system. PD patients with Pisa syndrome may have central, peripheral, or mixed vestibular dysfunction, while less data is available for camptocormia.[42,83] Vitale and collaborators described peripheral unilateral vestibular hypofunction ipsilateral to the leaning side and contralateral to the side that was most affected by PD in a small sample (n = 11) of patients with PD.[83] In PD with Pisa syndrome there may also be a bilateral alteration of cervical vestibular evoked myogenic potentials, pointing toward impairment of the vestibulospinal pathway.[58] A vestibular dysfunction in the roll plane may be associated with deviation of the subjective visual vertical,[37,44,46,48,57] estimated in about 67% of PD patients with Pisa syndrome.[65] A recent case–control study found worse performance on the subjective visual vertical perception in PD patients with Pisa syndrome compared to PD controls without axial postural abnormalities, but not in those with camptocormia when compared to their controls.[114] In the same study, reduced awareness of axial postural abnormality was observed in >60% of patients with PS or CC, suggesting a possible role for altered proprioception. There is a lack of available information for possible vestibular dysfunctions in patients with antecollis.

The control of posture is a semi-automated processing requesting a complex interaction between motor and cognitive networks, especially involving attentional and executive functions domains.[113] However, the association between cognitive

deficits and axial postural abnormalities remains controversial. In a small sample of PD, no difference in executive functions evaluated with the Montreal Cognitive Assessment and the Frontal Assessment Battery were recorded between patients with and without Pisa syndrome.[79] Two studies observed lower scores on tasks exploring executive functions, perceptual visuospatial functions, and language for patients with Pisa syndrome compared to those without axial postural abnormalities.[52,66] Only a few studies assessed the cognitive functions in patients with camptocormia compared with PD patients without postural abnormalities,[27,33,114] but none have specifically evaluated cognition in patients with antecollis. Whether these dysfunctions result from axial postural abnormalities or are a contributing factor remains to be investigated; nonetheless, there is growing evidence for the involvement of visuospatial abilities in patients with Pisa syndrome and not in camptocormia.[114]

Peripheral Mechanisms

Empirical findings show that myopathy has a homogenous but not specific appearance, and the etiology of myopathy remains unclear, but ongoing research marks it as a secondary myopathic process.[41] The data on the beneficial effects of deep brain stimulation on camptocormia[60] suggest a central process and secondary muscle damage caused by altered central control of body posture.[80] These phenomena probably reflect a continuum from early myopathic changes (ie, edema and swelling, contrast enhancement without degenerative muscle changes) in the early stages of camptocormia to progression to muscle atrophy and fatty degeneration in the end stage (ie, atrophy, fatty changes, marked connective tissue increase). In fact, the exact etiology of muscular changes is unclear. It is hypothesized that they may be the consequence of muscle disuse or denervation secondary to prolonged trunk misalignment driven by central mechanisms. Moreover, there is evidence that patients can present axial postural abnormalities without myopathic changes in the paraspinal and non-paraspinal muscles.[87,96]

A primary myopathy has been suggested to explain Pisa syndrome,[81] but no pathological studies are available to endorse this hypothesis. Tassorelli and colleagues found more pronounced muscular atrophy on the leaning side, with a craniocaudal gradient involving the multifidus and the latissimus dorsi muscles.[81] An MRI study confirmed atrophy of the lumbar paraspinal muscles with greater fatty degeneration more prevalent on the leaning side.[78] The observed muscular changes are probably caused by secondary mechanisms: the atrophy ipsilateral to the bending side may be due to muscle disuse, while contralateral muscle atrophy might be secondary to the stretching stress.[78]

Peak trunk extension force was much lower in PD patients with camptocormia than in healthy controls but did not differ from PD patients without camptocormia. However, the mechanical efficiency of muscular activation (especially at the thoracic level) of trunk extension was markedly reduced in PD patients with camptocormia compared to PD without postural alterations and to healthy controls, which suggests impairment of neuromuscular recruitment.[41] Clinically, patients with camptocormia can benefit from the support of a high-frame walker to support and re-align the trunk during stance and walking.[115] Further studies are needed to understand the role of muscular atrophy and weakness in PD patients with and without axial postural abnormalities.

Several methodological and technical problems limit the assessment of myopathy and have inevitably produced discrepancies between studies. Electromyography of the paraspinal muscles is technically difficult and findings from muscle biopsy and MRI studies may reflect age-related changes because there are no reliable age-matched control data in the literature.[116] For further research in empirically proven myopathic changes in trunk muscles, other more commonly available methods such as ultrasound are needed to monitor the time course of myopathy and related trunk misalignment in combination with age-matched control data. This is particularly important for informing treatment options.

Finally, axial postural abnormalities could be more frequent in patients with concomitant history of back surgery, degenerative spinal conditions or severe spine trauma.[5,33,43,79,82,87–90,95,96,106] These complications may have mechanical effects on bones or soft tissue, predisposing to the development of axial postural abnormalities.[117] Many patients complain of other symptoms, such as fatigue, pain (producing compensatory postures), and strenuous exercise.[88,91] The role of chronic pain, in particular, should be explored as a potential trigger of axial postural abnormalities in parkinsonism.[6,25,84]

Pathophysiology Clues from Therapeutic Approaches

There are anecdotal studies reporting on drug-induced axial postural abnormalities in people with parkinsonism. Many studies involving small patient samples have explored the relationship between the use of dopamine agonists and the onset of axial postural abnormalities. The subacute onset of axial postural abnormalities usually improved after withdrawal of the agonist. Antecollis has been observed to appear 2 weeks later after initiation of pramipexole and pergolide therapy in patients with PD.[118] Pisa syndrome has been observed after the initiation or a dose increase of dopaminergic medication such as levodopa, levodopa/carbidopa, levodopa/benserazide, and levodopa/carbidopa/entacapone[32] or the addition of rasagiline to levodopa treatment.[85] A reduction, switching to another dopaminergic medication or their withdrawal led to improvement of posture.[32] In non-PD patients the use of dopamine receptor blockers or cholinesterase inhibitors has been frequently associated with Pisa syndrome. Occasionally, Pisa syndrome appears after initiation of an antipsychotic or arises insidiously in antipsychotic-treated patients for unknown reasons.[119] These findings would indicate a central dysregulation of dopaminergic networks in the pathogenesis of axial postural abnormalities. However, in most cases of

axial postural abnormalities, there is no evidence of influence of the therapies on the onset or persistence of axial postural abnormalities in parkinsonian patients and whether the rare drug-induced cases of antecollis, camptocormia or Pisa syndrome should be considered a group apart is still a matter of debate.

Other clues from therapeutic studies endorsing the role of basal ganglia in sustaining axial postural abnormalities derive from the improvement in axial postural abnormalities after high-frequency deep brain stimulation of the bilateral subthalamic nuclei.[39,59,64] Also, repetitive trans-spinal magnetic stimulation of spinal pathways may have an immediate beneficial effect on camptocormia, according to one study.[77] Moreover, a possible neuronal dysfunction in the midbrain, as evidenced by tests of saccadic eye movement[90] and smaller midbrain axial surface,[89] has been observed in patients with camptocormia. Finally, case series observed the onset of Pisa syndrome to the right side following 4, 8, and 9 years after surgery (left pallidotomies) in patients with PD.[120]

Conclusions

The recognition of clinical predictors and pathophysiology of axial postural abnormalities in parkinsonism is far from being elucidated due to literature bias, encompassing different inclusion criteria and measurement tools, heterogeneity of patient samples and the common habit of considering axial postural abnormalities as a unique entity, without differentiating forward trunk flexion, lateral trunk flexion or forward neck flexion. While we were able to map out the current literature on axial postural abnormalities many research gaps still exist. To date, the most promising aspects to analyze are related to healthy (age-related) vs. PD-associated changes in posture, the role of rigidity of axial muscles on posture, and the impact of proprioception, the vestibular system, and higher cognitive functions. Also, the role of therapies acting on basal ganglia and dopaminergic networks needs to be clarified. Consensus among movement disorder experts on the nosology and the cut-off criteria for axial postural abnormalities has recently been reached,[4] and this can be a starting point for the harmonization of inclusion criteria in future studies.

Regarding risk factors for the development of axial postural abnormalities, the best literature evidence suggests that more severe motor symptoms, especially with higher involvement of axial symptoms, are associated with the development of both camptocormia and Pisa syndrome. At the same time, it is interesting as some PD nonmotor features like REM sleep behavior disorder or lower smell function have been associated with a higher probability of developing axial postural abnormalities. Altogether, these findings seem to suggest that a more severe PD phenotype can be at higher risk of developing these axial symptoms. The fact that the disease severity is linked to the development of axial postural abnormalities is also endorsed by many class IV evidence studies highlighting a correlation with higher Hoehn and Yahr stages and longer disease duration. Moreover, older age is another risk factor frequently reported in the literature.

Regarding pathophysiology, the highest evidence points toward an alteration of the visual vertical perception and the elaboration of multimodal information provided by basal-ganglia networks as pathogenic mechanisms associated with both Pisa syndrome and camptocormia. This evidence is also supported by the numerous studies showing an improvement of posture after deep brain stimulation. The role of vestibular system imbalance is also possibly implicated as well as the presence of peripheral abnormalities in axial muscles (both myopathic changes and strength alterations). The latter can be a consequence (eg, a peripheral process related to early-onset and short-lived dystonic phenomenon) or a trigger for the development of axial postural abnormalities when altered central integration of proprioceptive signals coming from the periphery are present.

However, current body of research holds more open questions than answers. Further studies on predictors, pathophysiology, management, and prevention of axial postural abnormalities are needed. In conclusion, systematic and standardized screening and assessment of axial postural abnormalities is recommended to provide patients with prompt treatment.[4] Prospective, long-term studies with large samples are urgently needed to explore the potential risk (casual) factors involved in their development.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

C.A.A.: 1A, 1B, 1C, 3A, 3B
C.G.: 1A, 1B, 1C, 3A, 3B
J.N.: 1A, 1B, 1C, 3B
C.A.: 1A, 1B, 1C, 3B
D.G.: 1B, 1C, 3B
M.L.D.: 1B, 1C, 3B
D.S.: 1B, 1C, 3B
Y.L.: 1B, 1C, 3B
M.A.W.: 1B, 1C, 3B
M.S.: 1B, 1C, 3B
R.W.: 1B, 1C, 3B
V.T.L.: 1B, 1C, 3B
G.I.: 1B, 1C, 3B
S.C.: 1B, 1C, 3B
M.M.: 1B, 1C, 3B
B.R.B.: 1B, 1C, 3B
T.C.: 1B, 1C, 3B

R.D.: 1B, 1C, 3B
K.D.: 1B, 1C, 3B
A.F.: 1B, 1C, 3B
H.T.: 1B, 1C, 3B
L.L.: 1B, 1C, 3B
N.G.M.: 1B, 1C, 3B
C.M.: 1B, 1C, 3B
Y.U.: 1B, 1C, 3B
R.B.: 1A, 1C, 3A, 3B
M.T.: 1A, 1B, 1C, 3A, 3B

Disclosures

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Main characteristics of studies on clinical predictors for axial postural abnormalities in patients with Parkinsonism.

Table S2. Main characteristics of studies on the pathophysiology of axial postural abnormalities in patients with Parkinsonism.

Data S1. Electronic search strategy.