Upper camptocormia in Parkinson's disease: neurophysiological and imaging findings of both central and peripheral pathophysiological mechanisms

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Word count:
Abstract: 235 words.
Main text: 4013 words.
Tables / Figures: 2 / 2.
Supplementary file: 1.
References: 33.

Key words:
Camptocormia; Parkinson's disease; pathophysiology; electromyography; magnetic resonance imaging.

ABSTRACT

Background: Camptocormia is a disabling complication of Parkinson's disease (PD), but its pathophysiology is poorly elucidated. Depending on the fulcrum of forward trunk flexion, two subtypes have been defined, upper (UCC) and lower camptocormia, the former being much more frequent. The aim of the study was to explore possible pathophysiological mechanisms of PD-related UCC.

Methods: Ten PD patients with UCC (UCC-PD) and ten PD patients without camptocormia (NoUCC-PD) underwent simultaneous electromyography (EMG) of thoracic paraspinal (TPS), obliquus externus abdominis (OEA), rectus abdominis (RA), and iliopsoas (IP) muscles during relaxed standing (both groups) and trunk realignment (UCC-PD group). Quantitative EMG and magnetic resonance imaging (MRI) of TPS muscles were also performed.

Results: UCC-PD patients showed hyperactivity of TPS and OEA muscles in quiet stance. During voluntary trunk extension, hyperactivity of OEA muscles persisted, thus revealing a co-contraction of flexor and extensor trunk muscles. Motor unit potentials (MUP) of TPS muscles showed shorter duration (p=0.005) and lower amplitude (p=0.004) in UCC-PD than in NoUCC-PD patients. MRI did not detect significant between-group differences in the cross-sectional area and fat fraction of TPS muscles, although the latter was higher in the UCC-PD than in the NoUCC-PD group at all thoracic levels.

Conclusion: Our findings suggest that hyperactivity of OEA might sustain UCC in PD. Concurrent mild myopathic changes in TPS muscles in PD with UCC may be secondary to muscle disuse but nevertheless may contribute to abnormal trunk posture.

INTRODUCTION

Camptocormia is an abnormal involuntary anteflexion of the thoracolumbar spine which becomes apparent when standing or walking and disappears in the recumbent position[1]. It is a disabling complication of Parkinson's disease (PD) and major therapeutic challenge due to poor response to dopaminergic treatment[1]. Two camptocormia subtypes are distinguished based on the fulcrum of forward bending[2]. A recent consensus-based proposal defined upper (UCC) and lower camptocormia (LCC) respectively as an anteflexion of minimum 45° at the thoracic fulcrum (C7 to T12-L1) and minimum 30° at the lumbar fulcrum (L1-sacrum, hip flexion), measured using a wall goniometer[3]. This classification is noteworthy as different muscles may be involved in determining UCC and LCC[2]. Bilateral obliquus externus abdominis (OEA) along with bilateral obliquus internus abdominis and rectus abdominis (RA) muscles are postulated to play a major role in UCC, whereas RA and iliopsoas (IP) muscles might be responsible for LCC.[2] Based on the classification criteria mentioned above, UCC has recently been reported as the most frequent camptocormia subtype in the PD population[4]. In parallel, an international consensus group of experts in movement disorders introduced a standardized method to measure camptocormia in standing patients[5]. Besides formulating the concepts of total camptocormia (TCC) and UCC angles, the former being the angle between the line joining the lateral malleolus to the L5 spinous process and the line connecting the L5 and C7 spinous process, they developed an app for their measurements[5].

The pathophysiology of PD-related camptocormia has been investigated over the last years but remains controversial[1,2,6]. Current evidence suggests the relevance of either central or peripheral mechanisms[1,2,6-19]. Specifically, centrally-induced camptocormia may depend upon axial dystonia determining an imbalance in the activity of flexor and extensor trunk muscles. Several observations support the dystonic hypothesis. Firstly, camptocormia sometimes improved after botulinum toxin (BoNT) or lidocaine chemodenervation targeting different hyperactive trunk muscles[7-13]. Recent studies showed that lidocaine[9,11,12] and BoNT[10,13] injections into OEA muscles resulted in mild to marked improvement of UCC in terms of camptocormia angle in PD patients whereas lidocaine chemodenervation of major psoas muscles had positive outcomes in LCC[11]. Secondly, few studies described positive responses of PD-related camptocormia to DBS[14,15]. Finally, camptocormia tends to resolve when leaning against a wall and was anecdotally reported to be relieved by wearing a backpack. These clinical signs were interpreted by some authors as possible sensory tricks, which are a hallmark of dystonia, either idiopathic or secondary[1,2,20]. Regarding the peripheral hypothesis, several studies reported evidence of paraspinal muscles myopathy as suggested by EMG and magnetic resonance imaging (MRI), which reflected camptocormia duration[16-19]. Histopathology of paraspinal muscles confirmed nonspecific myopathic changes, including variation in fiber size, increase in type-1 and reduction in type-2 fibers, fibrosis, and fatty degeneration[16-19].

Overall, most of the above-mentioned studies supporting one or other of the pathophysiological hypotheses preceded the consensus-based proposal to classify camptocormia in two subtypes as well as the recently standardized method to measure the TCC and UCC angles[3,5]. If different pathophysiological mechanisms underlie the two camptocormia subtypes, it is crucial to test them in distinct UCC and LCC cohorts. In this study we employed a multimodal approach, including clinical, EMG, and MRI evaluation, to explore the pathophysiology of PD-related UCC.

METHODS

Subjects

Ten PD patients with UCC (UCC-PD) were consecutively enrolled at the Movement Disorders Center of the University Hospital of Verona, Italy. Inclusion criteria were: a) clinically established PD according to the 2015 Movement Disorder Society diagnostic criteria, b) UCC defined as minimum 45° of non-fixed trunk anteflexion at the thoracic fulcrum on wall goniometer[3], c) modified Hoehn and Yahr stage <4 in the on-medication state. Exclusion criteria were: a) trunk laterodeviation >5°, b) moderate-severe tremor in the on-medication state, c) history of other neurological diseases, orthopedic diseases, and major spine surgery, d) ongoing anticoagulant therapy, e) history of exposure to antipsychotics, valproate, and anticholinergics, f) MRI contraindications. Ten age- and sex-matched PD patients without camptocormia (NoUCC-PD) who were eligible for needle EMG (nEMG) and MRI were recruited as controls. Clinical assessment, EMG, and MRI were performed when participants were in the on-medication state to minimize variability due to motor fluctuations. We excluded patients with moderate-severe tremor in the on-medication state in order to minimize the risk of electrodes' dislocation during EMG evaluation in dynamic upright positions and to avoid tremor artifacts in the EMG recording, which would have hampered the interpretation of quantitative data. All participants gave informed consent to participate in this study, which was approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Clinical assessment

The following information was collected: age, sex, height, weight, PD duration, PD phenotype (tremor-dominant or akineto-rigid), ongoing anti-parkinsonian therapy, and levodopa equivalent daily dose (LEDD). We performed a thorough neurological examination and determined the Unified Parkinson's Disease Rating Scale Part III score (UPDRS-III) and the subscore for axial features using the following items: speech (item 3.1), neck rigidity (3.3a), rising from a chair (3.9), gait (3.10), postural stability (3.12), and posture (3.13)[21]. The 8-item PD Questionnaire (PDQ-8) and Montreal Cognitive assessment (MoCA) were administered. Photos of the standing UCC-PD patients were evaluated through CamptoApp® to calculate the camptocormia angles[5]. In UCC-PD patients we recorded fulcrum of trunk anteflexion, latency between PD and UCC onset, UCC duration, presence of back pain, and awareness of UCC.

EMG evaluation

EMG evaluation was performed by the same examiner using a Keypoint EMG system (Dantec, Skovlunde, Denmark; filters 20-10.000 Hz). The EMG protocol included three parts, taking approximately 60 minutes.

1) Simultaneous EMG recordings from bilateral thoracic paraspinal (TPS; T9 level), OEA, RA, and IP muscles were obtained using fine-wire electrodes (FU50M20, SEI EMG, Padua, Italy) with a bipolar montage. Fine wire electrodes were inserted bilaterally as follows:
   - TPS muscle: 3 cm lateral to the spinous process of the T9 vertebra;
   - OEA muscle: 5 cm above the anterior superior iliac spine in the anterior axillary line;
   - RA muscle: 3 cm lateral to the *linea alba*, 3 cm above the umbilicus;
   - IP muscle: 3 cm lateral to the femoral artery pulse, 1 cm below the inguinal ligament.

   Placement of electrodes in the TPS muscles was performed while patients were lying in the prone position on an EMG bench, whereas placement of electrodes in the EOA, RA, and IP muscles was performed while they were lying in the supine position. Ultrasound guidance allowed accurate electrode positioning. In both groups, we did not detect any EMG activity at rest, and voluntary activation of the studied muscles confirmed the right placement of the electrodes. EMG cables were fixed to the patients' thoracic and abdominal wall by a piece of adhesive tape in the portion closest to the electrode in order to minimize the risk of its dislocation.

   In the UCC-PD group, EMGs were recorded in two conditions: a) during unsupported relaxed standing in the usual camptocormic posture (30 seconds); b) during maximal voluntary trunk extension in stance to obtain trunk realignment under clinical supervision (three trials, 10 seconds/trial). NoUCC-PD patients were only assessed during quiet standing. Hyperactivity of a given muscle was defined as high tonic activity during conditions characterized by physiological EMG silence (at rest or during voluntary activity of antagonistic muscles). The EMG pattern was also recorded from different muscles in two healthy subjects during relaxed standing and trunk extension.
2) EMG activity of bilateral TPS muscles was quantitatively evaluated. Raw EMG data recorded using fine-wire electrodes were full-wave rectified and smoothed with a 1-second root mean square (RMS) window. For each patient, the highest and most symmetrical RMS amplitude recorded from TPS muscles during 30 seconds of unsupported quiet standing was normalized to the individual highest and most symmetrical RMS amplitude recorded from the same muscles during maximal voluntary contraction (MVC). The activity level of TPS muscles in relaxed standing was therefore expressed as a percentage of this maximal signal (%MVC)[22]. MVC of TPS muscles was obtained by asking patients lying prone on a physiotherapy bench with their arms at their side and pelvis immobilized to extend the trunk against manual resistance while receiving verbal encouragement to exert a maximum effort. The motor task was performed three times (10 seconds/trial).

The correct placement of EMG electrodes was checked by the examiner at the end of parts 1 and 2 of the EMG evaluation by asking the patients to perform a voluntary muscle activation.

3) All subjects underwent motor unit potential (MUP) analysis (multi-MUP analysis) of bilateral TPS muscles at the T9 level. Concentric needle electrodes (F8990/37, Fiab SpA, Florence, Italy) and the automated multi-MUP program analysis were used. Participants lay in prone position keeping their arms by their sides of the body and were asked to perform a slight albeit constant force extension of the head and trunk so that 20 non-duplicate MUPs per side were obtained after editing, according to a standardized method[23]. Mean MUP duration and amplitude, and the percentage of polyphasic MUPs were collected.

MRI scanning

All participants underwent non-contrast 1.5T spine MRI (Ingenia, Philips Medical Systems, Eindhoven, The Netherlands) with a phased array coil. The MRI protocol included: 1) T2 weighted turbo spin echo (TSE) sagittal, slice thickness (SL) 3 mm, repetition time/echo time (TR/TE) 4875/120 ms, TSE factor 21; 2) T1 weighted TSE axial (flip angle 90°), SL 5 mm, TR/TE 547/15 ms; 3) Short tau inversion recovery (STIR) axial (no angulation), SL 5 mm, TR/TE/inversion time (TI) 4875/120/140 ms, TSE factor 21; and 4) Gradient echo (GRE) axial (flip angle 15°) type Dixon 2-point, SL 4 mm, TR/TE 1,8/4 ms. Axial T1-weighted, STIR and GRE Dixon images were acquired in two overlapped stacks, covering the whole thoracolumbar spine. The Dixon method provided four images ("in-phase", "out-of-phase", "water-only", "fat-only"). Dixon "fat-only" images were binarized with the Otsu's algorithm. Regions of interest (ROIs), i.e. axial cross-sectional areas of bilateral TPS muscles at levels T1-T3-T5-T7-T9-T11, were manually defined on Dixon "in-phase" images using the ImageJ software[24]. ROIs were overlaid onto corresponding binarized Dixon "fat-only" images, where hyperintense voxels represented fat tissue, in order to calculate the fraction of fatty infiltration within muscle tissue (fat fraction, FF). The severity of muscle edema, defined as hyperintense signal within TPS muscles in minimum two contiguous axial slices in the short-tau inversion-recovery sequence, was semi-quantitatively scored as follows: not present (0), mild (1, slight hyperintensity), or severe (2, pronounced hyperintensity). An edema score was calculated by multiplying edema severity by its rostro-caudal extensiveness for each side (unilateral score) and for both sides as a sum (bilateral score)[19].

Statistical analysis

Absolute and relative frequencies were calculated for dichotomous variables and tested by Fisher's Exact test. For continuous data, descriptive statistics is reported as means ± standard deviations and between-group comparisons were performed using nonparametric Mann-Whitney U test due to the small sample size. For %MVC, MUP parameters, and MRI data, inter-side differences were explored in each group through the Wilcoxon rank-sum test and, as they were not significant, data from the two sides were averaged before inter-group comparisons. Correlations were explored with nonparametric Spearman's ρ coefficients. An alpha level $p \leq 0.05$ (two-tailed) was regarded as significant difference. Statistical analyses were carried out using SPSS® Statistics for Macintosh (version 21.0).

RESULTS

Clinical data

Demographic and clinical features of UCC-PD (7 males, 3 females) and NoUCC-PD (6 males, 4 females) patients are summarized in Supplementary Table 1.

Comparisons between UCC-PD and NoUCC-PD patients showed no differences in age (mean UCC-PD group: 72.3±7.8 years; mean NoUCC-PD group: 70.2±6.1 years; p=0.393), body mass index (mean UCC-PD group: 23.9±3.7 kg/m^2; mean NoUCC-PD group: 25.3±3.9 kg/m^2; p=0.579), PD duration (mean UCC-PD group: 5.6±4.0 years; mean NoUCC-PD group: 7.0±5.0 years; p=0.739), UPDRS-III axial in the on-medication state (mean UCC-PD group: 5.8±3.6; mean NoUCC-PD group: 3.1±2.4; p=0.063), LEDD (mean UCC-PD group: 479.5±217.5 mg/day; mean NoUCC-PD group: 520.7±278.3 mg/day; p=1.000), PDQ-8 (mean UCC-PD group: 17.8±13.5; mean NoUCC-PD group: 19.1±14.5; p=0.631), and MoCA (mean UCC-PD group: 23.3±4.0; mean NoUCC-PD group: 25.4±2.8 ; p=0.353). Dopaminergic treatment achieved satisfying limb motor control in all patients. In both study groups, five out of ten patients (50%) were taking dopamine agonists (Supplementary Table 1). We did not notice any dystonic features (i.e., cranio-cervical or limb dystonia and/or jerky tremor possibly consistent with dystonic tremor) in the study patients during their clinical assessment. None of the study subjects was on deep brain stimulation.

In the UCC-PD group, at the time of assessment, the mean UCC duration was 2.9±3.2 years and the mean latency between PD and trunk anteflexion onset was 2.7±1.8 years. The mean UCC angle measured using CamptoApp® was 48.5±3.9°, whereas the mean TCC angle was 20.0±4.5°. Camptocormia did not respond to patients' individualized optimal dose of anti-parkinsonian medications. Patients in the UCC-PD group did not receive any treatment specifically addressing their postural abnormality prior to or during the study, including off-label treatments (i.e., botulinum toxin or lidocaine injections into trunk muscles) nor any trunk-specific rehabilitation program. Back pain was reported by four UCC-PD patients, with a mean numeric rating scale of 2.1±3.1. There was no evidence of gestures possibly consistent with sensory tricks. The severity of UCC documented by the UCC angle correlated with the intensity of back pain (ρ=0.674, p=0.033) but not with PD and UCC duration, PD phenotype, UPDRS-III, UPDRS-III axial, and LEDD.

In the NoUCC-PD group, five patients presented with normal posture, four patients with stooped posture, and one patient with stooped posture associated with 5-degree left trunk laterodeviation. None of them had experienced any major postural deformity, thus being their absence not attributable to the response to any ongoing medication nor to the discontinuation of any previous medication (e.g., dopamine agonists).

EMG findings

Simultaneous EMG recordings of flexor and extensor trunk muscles during relaxed standing revealed a common EMG pattern of muscle activity in all but one UCC-PD patients (cases 1-9; Figures 1-2). EMG activity was considered to be hyperactive ["EMG(+)"] or comparable ["EMG(-)"] relative to that of healthy

subjects at baseline level. The common EMG pattern was characterized by hyperactivity of bilateral TPS and OEA muscles. The remaining UCC-PD patient (case 10; Figure 1) showed hyperactivity of bilateral TPS but not OEA muscles during quiet standing. Hyperactivity of bilateral TPS muscles was also detected in 8 PD patients without UCC (cases 11-16,19,20; Figure 1). Case 15 showed hyperactivity of the left OEA muscle, which was consistent with mild left laterodeviation of the trunk (5°). In the remaining two NoUCC-PD patients (cases 17-18; Figure 1), there was not hyperactivity in the assessed muscles.

During voluntary trunk extension to obtain trunk realignment (Figures 1-2), hyperactivity of OEA muscles observed in nine UCC-PD patients (cases 1-9) did not decrease, thus resulting in a co-activation of antagonistic muscles, i.e. TPS (trunk extensors) and OEA (trunk flexors) muscles (Figures 1-2). Moreover, in four of them, voluntary trunk extension to realign the trunk resulted in a paradoxical tonic activation of other flexor trunk muscles, that is the RA muscle, either unilaterally (case 3) or bilaterally (case 1), and the IP muscle, either on one side (case 4) or both (case 8). We did not detect paradoxical activation of OEA, RA, and IP muscles in UCC-PD Patient 10 nor in two PD patients without UCC (cases 19-20) who were additionally asked to perform a trunk hyperextension during standing (not shown).

There was no significant between-group difference in the normalized EMG activity of TPS muscles during unsupported quiet standing, although %MVC showed higher values in UCC-PD patients than in NoUCC-PD patients (Table 1).

NEMG of TPS muscles did not detect spontaneous activity from denervation. Multi-MUP analysis revealed that mean MUP duration was significantly shorter (p=0.005) and mean MUP amplitude significantly lower (p=0.004) in the UCC-PD group than in the NoUCC-PD group, whereas no between-group difference existed in the percentage of polyphasic MUPs (Table 1).

There was no correlation between %MVC or MUP parameters and clinical variables related to PD and UCC nor between %MVC and MUP parameters.

MRI findings

No significant between-group differences existed in the cross-sectional area and FF of TPS muscles at the T9 level (Table 1) and in all other thoracic levels investigated (Table 2). However, higher FF values were detected in the whole thoracic segment (Table 2). In the UCC-PD group, the area of TPS muscles at the T9 level negatively correlated with the FF at the same level (ρ=-0.709, p=0.022) and UCC severity documented by the UCC angle (ρ=-0.930, p<0.001), and a positive correlation existed between FF of TPS muscles at the T9 level and the UCC angle (ρ=0.766, p=0.010).

Edema of TPS muscles was detected in four out of ten (40%) UCC-PD patients and two out of ten (20%) NoUCC-PD patients (Fisher's Exact test p=0.628). When considering only patients with edema, the bilateral edema score was 21.5±3.0 in UCC-PD and 19.0±7.1 in NoUCC-PD patients (p=1.000). In the UCC-PD group, we did not find correlations between the presence and severity of muscle edema and clinical variables related to PD or UCC, %MVC, MUP parameters, and other radiological findings.

DISCUSSION

In this study, 10 UCC-PD and 10 NoUCC-PD patients underwent clinical assessment, qualitative EMG of trunk muscles, and quantitative EMG and MRI of TPS muscles. Only UCC-PD patients showed EMG hyperactivity of TPS and OEA muscles during standing that persisted during voluntary trunk realignment, also involving often other trunk flexor muscles. Compared to the NoUCC-PD group, UCC-PD patients showed MUPs of shorter duration and lower amplitude in TPS muscles, with evidence of fatty infiltration on MRI. Overall, we provided evidence of co-contraction of antagonist trunk muscles when performing a forced trunk extension, but also of subtle myopathic changes in UCC.

Muscle co-contraction is a feature of many disorders of muscle hyperactivity, including dystonia. Trunk dystonia has been reported as possible contributor of PD-related camptocormia[1,2,11]. However, only two studies have hitherto assessed simultaneous activity of trunk muscles to investigate PD-related camptocormia using surface EMG[11,25]. Furusawa recorded EMG hyperactivity in the OEA muscle, either unilaterally or bilaterally, in ten out of eleven UCC-PD patients, which started before the appearance of camptocormia during verticalization on a tilt table[11]. Margraf documented high-amplitude EMG activity in OEA and rectus femoris but not RA muscles in ten PD patients with camptocormia[25]. Both studies documented hyperactivity of paraspinal muscles in camptocormic PD patients compared to controls[11,25]. Our findings from multichannel EMG using fine-wire electrodes complemented these two studies. Besides confirming the existence of OEA and paraspinal muscles hyperactivity in camptocormic PD patients during standing, we documented the persistence of OEA activation during voluntary trunk realignment. The OEA plays a role in both flexion and rotation of the spine. Indeed, bilateral contraction of OEA produce truncal forward flexion, while contraction of the same muscle on one side produces truncal homolateral flexion and rotation to the opposite side[26]. Here we hypothesize that hyperactivity of OEA when trying to correct trunk forward bending might be a critical factor in sustaining UCC. This hypothesis is supported by the evidence that medications which reduce muscle hyperactivation, such as lidocaine and BoNT,[9-13] may improve UCC. In only one UCC-PD patient we did not detect activity of OEA muscles. Although we cannot exclude technical limitations, this patient interestingly had a 3-month history of rapidly progressive trunk anteflexion and MRI revealed severe edema of TPS muscles (edema score=24), possibly suggesting a different culprit of UCC (e.g., focal myositis)[6,21].

Regarding other examined muscles, we did not detect pathological EMG activity in RA muscles during quiet standing, which is consistent with previous EMG observations[8,25] and reports on the inefficacy of BoNT and lidocaine chemodenervation targeting RA muscles in some PD patients with camptocormia[27,28]. Moreover, no abnormal EMG activity was recorded from IP muscles, whose physiological role is lumbar spine flexion at the hip[26]. This may reflect the exclusive enrollment of PD patient with UCC, who have more rostral fulcra of trunk anteflexion[3], and is supported by previous reports[8,27,28].

Normalized EMG activity of paraspinal muscles during standing was quantified in two previous studies enrolling PD patients[25,29]. Notably, Margraf found significantly higher activation of back muscles in

camptocormic PD patients than healthy controls and demonstrated that the functional reserve of these muscles was used to counteract the bending force in camptocormia[25]. In our study, activation of TPS muscles in quiet standing did not significantly differ between UCC-PD and NoUCC-PD patients, but higher albeit not significant %MVC was observed in the former, which reflects the need to recruit a higher number of motor units to maintain the upright posture[25].

By first performing multi-MUP analysis of TPS muscles in PD-related camptocormia, we found that MUPs of TPS muscles have significant shorter duration and lower amplitude in UCC-PD than NoUCC-PD patients. The interpretation of these findings is complex. However, since shortening of MUP duration reflects random loss of muscle fibers and is considered the most robust indicator in myopathic conditions[30], our data might reveal subtle myopathic changes in TPS muscles of UCC-PD patients compared to NoUCC-PD controls. This also parallels MRI evidence of higher, albeit not significantly, fatty infiltration of TPS muscles in UCC-PD than NoUCC-PD patients and positive association between FF and severity of UCC.

Previous literature suggests either a primary or secondary focal myopathy of paraspinal muscles in PD-related camptocormia, including under-use myopathy due to axial rigidity and overuse myopathy, but histopathological findings are not conclusive[1,2,6,16-19,31]. We speculate that subtle myopathic findings on multi-MUP analysis and MRI of TPS muscles might be secondary to the chronic imbalance between their eccentric and concentric contraction in order to counteract trunk anteflexion[11,26]. Repetitive contraction of elongated muscles produces elevated force output with low metabolic demand and was related to muscle damage[32]. Interestingly, this might parallel non-specific histological muscle changes in PD-related camptocormia, such as reduction in type-2 fast-twitch fibers and hypertrophy of fatigue resistant type-1 fibers, ultrastructural myofibrillar disarrangement, and defects of oxidative enzymes, as previously documented[16-19,31].

The controversy in the literature on whether dystonia or myopathy might be the cause of camptocormia in PD has been around for some time and still is an unresolved issue[1,2,6,7]. The evidence of co-contraction of trunk paraspinal muscles and OEA when standing up and during voluntary trunk realignment does not necessarily mean that camptocormia in PD is sustained by dystonia. Indeed, co-contraction is just one among the main phenomenological features of dystonia[33]. Yet, it should be noted that the myopathic changes found in the paraspinal muscles in our cohorts were mild and demonstrated only by quantitative MUP analyses. In addition, MRI data in the paraspinal muscles did not differ significantly between groups. For this reason, it is tempting to hypothesize that myopathic changes might not drive the onset of camptocormia in PD, but rather they are a contributing factor. The reason why co-contraction and myopathic changes might occur in the same PD patient with camptocormia is unknown and our study in unable to provide an explanation.

Our study has several limitations. First, the small sample size due to the complex and highly demanding protocol, which restricted enrollment to cooperative PD patients with no contraindications to nEMG and MRI. Second, the exclusion of PD patients with LCC, which impeded any generalization of our findings to the overall PD-related camptocormia. Third, the lack of a healthy control group due to ethical issues raised

by the use of invasive nEMG. This limits interpretation of multi-MUP analysis and Dixon-based MRI, for which normative values were not available. Fourth, we could not simultaneously record more than four muscle pairs due to limits of the EMG equipment, thus excluding other muscles possibly involved in UCC genesis. Fifth, we did not perform a time-based EMG analysis showing the order of muscle activation in the standing position before and after the appearance of UCC. Finally, EMG activity during trunk hyperextension and simulated flexed body posture was not assessed in the NoUCC-PD group. Nevertheless, nEMG first allowed an accurate study of trunk muscles in camptocormia, and multi-MUP analysis and Dixon-based MRI provided quantitative and reproducible data for future research.

In conclusion, our findings fuel the notion that hyperactivity of OEA muscles might sustain PD-related UCC, therefore suggesting EMG evaluation of these muscle as potential target for chemodenervation. Although findings from multi-MUP analysis and MRI need further confirmation, we proposed that concurrent mild myopathic changes in TPS muscles detected in PD patients with UCC may be secondary to muscle disuse but nevertheless may contribute to their abnormal trunk posture.

Acknowledgements

The Authors would like to thank Diego Cavalli and Giuditta Todesco for their contribution in collecting MRI data.

Funding

This study was supported by the Brain Research Foundation Verona O.N.L.U.S (Grant number 2017).

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Figure Captions

Figure 1. Simultaneous EMG recordings from flexor and extensor trunk muscles in PD patients with and without UCC during relaxed standing (part I, left) and voluntary trunk extension to obtain trunk realignment (part II, right; UCC-PD group only)

Legend: (+) = EMG hyperactivity; (-) = EMG activity comparable to that of healthy subjects, which was considered as baseline level (Figure 2).
Abbreviations: EMG = electromyography with fine wire electrodes; IP = iliopsoas muscle; *n* = unit; NoUCC-PD = patients with Parkinson's disease without camptocormia; OEA = obliquus externus abdominis muscle; RA = rectus abdominis muscle; TPS T9 = thoracic paraspinal muscle at the T9 level; UCC = upper camptocormia; UCC-PD = patients with Parkinson's disease and upper camptocormia.

Figure 2. Main pattern of EMG muscle activity in one representative UCC-PD patient during relaxed standing (left) and voluntary trunk extension to obtain trunk realignment (right)

Above. EMG traces recorded from TPS, OEA, RA, and IP muscles in a PD patient with UCC (case n. 6) during relaxed standing (left) and voluntary trunk extension to obtain trunk realignment (right). The patient was asked to breathe quietly throughout the evaluation. Below. EMG traces recorded from the same muscles in one representative healthy subject during quiet standing and voluntary trunk hyperextension.
Abbreviations: EMG = electromyography with fine wire electrodes; IP = iliopsoas muscle; L = left; OEA = obliquus externus abdominis muscle; R = right; RA = rectus abdominis muscle; TPS T9 = thoracic paraspinal muscle at the T9 level; UCC = upper camptocormia; UCC-PD = patient with Parkinson's disease and upper camptocormia.

Supplementary File Caption

Supplementary Table 1. Demographic and clinical characteristics of PD patients with and without UCC enrolled in the study