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Short communication

Cervical dystonia patients display subclinical gait changes

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ABSTRACT

Introduction: Gait disorders in cervical dystonia (CD) are reported in patients under DBS or in severe cases complicated with spinal deformities.
Objective: to assess walking motor pattern in CD patients without DBS and not presenting scoliosis.
Methods: Computerized gait analysis (CGA) was performed in CD patients, before and after botulinum toxin (BoNT) injections, and in healthy controls (HC). Spatiotemporal (ST) parameters were compared between CD and HC groups. Correlation analysis was conducted between ST parameters and clinical features of CD patients.
Results: CD patients demonstrated a significant reduction of velocity, stride length, % of swing phase, and dynamic stability index while stride and swing time were increased. No significant effect of BoNT was detected. A significant inverse correlation was found between TWSTRS and stride length.
Conclusion: CD patients may have a slow gait with subclinical evidence. Our data suggest this alteration might be an endophenotipic feature of CD.

1. Introduction

Cervical dystonia (CD) is one of the most frequent forms of focal dystonia predominantly presenting with a combination of tilting and rotation of the head [1]. Severe CD can be complicated by spinal deformities, such as scoliosis, that can afterwards impair walking [2]. Presently there are few studies addressing gait pattern in CD. Previous computerized gait analysis (CGA) studies in dystonia have only described gait abnormalities occurring in patients with focal forms (including CD) under pallidal deep brain stimulation (DBS) [3]. The mechanism of gait abnormalities triggered by DBS in these patients is unknown, and hypothesized to be due to the spreading of electricity towards the cortico-spinal tract or by an 'anti-kinetic' effect of stimulation itself, as described in PD patients [4]. A description of gait pattern in CD patients without DBS and with no clinical evidence of spinal deformities could therefore be of interest. The aim of the present study is to objectively assess the gait pattern – particularly the spatiotemporal (ST) parameters – of these patients. Although CD patients do not clinically display a walking impairment, our approach may identify subclinical gait abnormalities representing a specific feature of this movement disorder. Furthermore, as the gait of CD patients might be impaired by abnormal head posture, we explored whether successful treatment with botulinum toxin (BoNT) may result in gait changes.

2. Patients and methods

Consecutive patients with isolated idiopathic CD followed in our BoNT clinic were enrolled. All participants gave written informed consent prior to their inclusion. Patients with clinical evidence of spinal deformities, pyramidal signs or other conditions potentially impairing gait were excluded. All patients have been evaluated with Adam's forward bend test in order to exclude thoracic and lumbar curves [5] and only patients with a Cobb angle measuring less than 20° were included. Clinical data collected included disease

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duration, BoNT treatment duration, clinical phenotype and severity measured with the severity subscale of the Toronto Western Spasmodic Torticollis Rating scale (TWSTRS) [6]. The walking of 13 CD patients was analyzed by an opto-kinetic 3D gait analysis (BST GAITLAB, BST SMART DX 6 TVC, Milan, Italy) at least three months after the last treatment with BoNT (CD group). Eight patients underwent a repeated CGA 4 weeks after the last treatment with BoNT to control for possible changes of gait related to the correction of head deviation following injections (CDpost group). The same assessments were performed in 19 healthy subjects as control group (HC group) and 12 of them underwent a repeated assessment during which they were asked to walk with the head rotated 45° (6 towards the right side and 6 towards the left) (HCht group). All groups were matched for age and sex.

Parameters of gait were detected using the Davis protocol [7]. The recorded temporal parameters were: stance time, double support time, stride time and cadence. The following spatial parameters were analyzed: stride length, step width, step length, step asymmetry (defined as the ratio between right and left step length) and velocity. The dynamic stability index, calculated as the ratio between single and double support time, was also calculated. Coefficient of variation (CV) was calculated for swing phase, stride length and time.

2.1. Statistical analysis

Descriptive statistics were computed using IBM SPSS Statistics (version 22 for Windows). Group matching regarding age and gender was tested by unpaired *t*-test and $\chi 2$ respectively. As assessed by the Shapiro-Wilk test all data did not meet the assumption for normality apart from TWSTRS score. Accordingly, the Mann-Whitney *U* test was used to compare CD with HC and HCht. Within group comparisons (CD vs. CDpost and HC vs. HCht) were performed using a Wilcoxon paired test. In order to minimize the possibility of a type 1 error, we set statistical significance at $p < 0.0167$ after Bonferroni correction for multiple comparisons. A nonparametric correlation analysis (Spearman rank test) was used to correlate instrumented gait measures with disease duration, whereas a parametric correlation (Pearson test) was adopted to correlate TWSTRS score (normally distributed) with gait variables, which were log transformed. In the correlation analysis, we took into account only the gait parameters that were significantly different between CD patients and HC after correction for multiple comparisons.

3. Results

3.1. Demographic and clinical data

This study included 13 patients with idiopathic CD presenting the following phenotypes: 4 torticollis, 7 laterocollis and 2 retrocollis. Details of Demographic and clinical data are reported in Table 1.

3.2. Computerized gait analysis

Since right versus left values were not significantly different for all ST parameters within each group, we analyzed the averaged value. In comparison with both HC and HCht, CD patients were found to have a significantly reduced velocity, stride length, % of swing phase, and dynamic stability index; the CV of stride and swing times of CD patients were significantly increased compared to HC; finally, cadence and step length was reduced in CD patients only when compared to HCht (Fig. 1, Table 1). The remaining parameters assessed did not differ significantly across groups (Table 1). Statistical analysis did not demonstrate any significant differences between HC and HCht and between CD and CDpost despite clinical improvement indicated by a significant TWSTRS score reduction 4 weeks after the treatment with BoNT (Supplemental material online – Tables 1 and 2).

3.3. Correlation analysis

A significant inverse correlation was found between the TWSTRS score and stride length ($\rho = -0.703$; $p = 0.044$ correction for multiple comparison). No other significant correlations were detected (Supplemental material online – Table 3).

4. Discussion

This study demonstrates that patients with idiopathic and isolated CD have subtle and subclinical gait abnormalities including increased variability and lower velocity. We believe that such abnormalities are associated with the neuronal dysfunction leading to dystonia and do not merely reflect the detrimental result of head deviation, e.g. due to abnormal posture or its influence on the vestibular system. In fact, posture changes after BoNT did not alter gait parameters in CD patients and no detrimental effect of forced head deviation was detected in HC. Furthermore, we found a significant inverse correlation between dystonia severity and stride length.

Several hypotheses can be formulated to explain our findings. Although isolated idiopathic CD is a disorder that affects only the neck muscles with possible spread to the face and less frequently the upper limb [8], a subtle concomitant lower limb involvement cannot be ruled out. In addition, patients with a long history of CD may develop spinal deformities with severe scoliosis producing gait difficulties, as already reported [9]. However, patients in this study did not present clinical evidence of spinal deformities nor pyramidal signs possibly indicating a subclinical myelopathy. We excluded patients with lumbar and thoracic curves measuring more than 20° as a previous study demonstrated that subjects with mild scoliosis (Cobb angle <20°) only present slight step length and stance phase reduction when assessed by CGA [2].

Our study demonstrates that patients with CD have walking abnormalities similar (although not clinically evident) to the ones seen in Parkinsonian gait [10]. In keeping with a subtle instability along the antero-posterior axis, our patients were found to walk at a slower pace, with shorter steps and spending a relatively higher time on double limb support. These results are in agreement with a previous study reporting a low self-balance confidence in CD patients, who were also found to have a reduced preferred walking speed [11].

The lack of detrimental effect of forced head deviation in HC as well as the lack of gait pattern change after BoNT treatment suggest that the underlying mechanism of CD abnormal gait might not be associated with the postural alterations caused by head and neck deviation as they are well controlled by BoNT injections [12]. Therefore, it is reasonable to consider that basal ganglia dysfunction originating focal dystonia may contribute the observed walking pathophysiology of CD patients.

Hypokinetic gait has been reported after pallidal DBS in a number of operated patients with focal dystonia, including CD [3]. There are few interpretations of this effect of DBS, though some authors suggest that globus pallidus internus stimulation may interfere with basal ganglia control of automatic gait. Our evidence of a slow gait even in unoperated CD patients may also support the role of a basal ganglia dysfunction in walking abnormalities and further suggest that gait disorder may be an endophenotipic feature of idiopathic CD, possibly revealed by DBS.

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Table 1
Demographic, clinical data and gait parameters of patients with cervical dystonia (CD), healthy controls (HC) and HC with turned head (HCht).

	CD (n = 13)	HC (n = 19)	HCht (n = 12)	p value (CD vs HC)	p value (CD vs HCht)	p value (HC vs HCht)
Demographic & clinical data						
Age (y)	59.1 ± 10.9	55.5 ± 5.7	56.58 ± 6.13	ns	ns	ns
Sex (m/f)	6/7	12/7	9/4	ns	ns	ns
Disease duration	7.7 ± 10.1	na	na			
BoNT treatment duration	3.4 ± 2.9	na	na			
BoNT mean dose (U.I.)[a]	400 ± 100	na	na			
TWSTRS	16.15 ± 4.4	na	na			
Spatiotemporal parameters						
Cadence (steps/min)	96.36 ± 3.25	104.35 ± 3.59	105.00 ± 2.54	ns	**0.004**	ns
Step length (m)	0.52 ± 0.02	0.66 ± 0.03	0.67 ± 0.03	ns	**0.003**	ns
Step asymmetry	0.98 ± 0.03	1.03 ± 0.01	1.02 ± 0.01	ns	ns	ns
Step width (%)	0.18 ± 0.01	0.15 ± 0.05	0.12 ± 0.02	ns	ns	ns
Stride time (s)	1.25 ± 0.04	1.15 ± 0.03	1.15 ± 0.03	ns	ns	ns
Stance time (s)	0.79 ± 0.03	0.72 ± 0.04	0.68 ± 0.05	ns	ns	ns
Swing time (s)	0.46 ± 0.01	0.46 ± 0.01	0.44 ± 0.01	ns	ns	ns
Double support time (s)	0.15 ± 0.01	0.12 ± 0.01	0.11 ± 0.01	ns	ns	ns
Stance time (%)	63.05 ± 1.48	60.52 ± 0.85	59.53 ± 0.63	ns	ns	ns
Swing time (%)	36.71 ± 0.50	39.47 ± 0.86	39.61 ± 0.53	**0.001**	**0.001**	ns
Double support time (%)	12.75 ± 1.02	11.35 ± 0.65	10.30 ± 0.59	ns	ns	ns
Stride length − CV	4.47 ± 0.61	2.39 ± 0.17	2.36 ± 0.51	ns	ns	ns
Swing time − CV	4.29 ± 1.48	1.85 ± 1.01	2.29 ± 2.71	**0.001**	ns	ns
Stride time − CV	4.34 ± 1.65	2.24 ± 1.51	2.18 ± 0.66	**0.011**	**0.001**	ns
Velocity	0.82 ± 0.18	1.15 ± 0.22	1.20 ± 0.17	**0.002**	<**0.001**	ns
Stride length	1.09 ± 0.07	1.33 ± 0.13	1.35 ± 0.08	<**0.001**	<**0.001**	ns
Stability index	1.77 ± 0.93	4.31 ± 1.16	4.08 ± 1.21	<**0.001**	<**0.001**	ns

Demographic and clinical data are reported as mean ± SD (standard deviation); Spatiotemporal parameters are reported as median±SE (standard error); Mann-Whitney test for comparisons group CD vs group HC and group CD vs group HCth, Wilcoxon-test for comparison group HC vs group HCth.
BoNT: botulinum toxin; TWSTRS: Toronto Western spasmodic torticollis rating scale; na = not applicable; ns = not significant; CV = coefficient of variation; m = male; f = fem. Significant values are reported in bold.
[a] Abobotulinumtoxin (Dysport™).

In conclusion, this study demonstrates that patients with isolated idiopathic CD might present subtle, sub-clinical and endophenotypical walking abnormalities consistent with a hypokinetic gait. The major limitation of our study is the small sample size and the fact that second condition was always performed after BoNT (with patients more comfortable with the experimental set up). A similar limitation applies to HCht as they all repeated the assessment after the first evaluation with straight head position, thus explaining the subtle improvement of their gait parameter (practice effect). This result may further rule out the contribution of postural alterations on gait parameters. Furthermore another limitation of our study is that we cannot rule out a possible detrimental effect on gait resulting from prolonged BoNT treatment. Future studies with larger samples are needed to confirm our findings in patients who have never received BoNT injections and comparing DBS patients (under different stimulation conditions) with unoperated CD patients. Finally, enrolling patients with other types of dystonia would also be of interest. Overall, this and future studies will certainly help understanding the pathophysiology of basal ganglia control of gait.

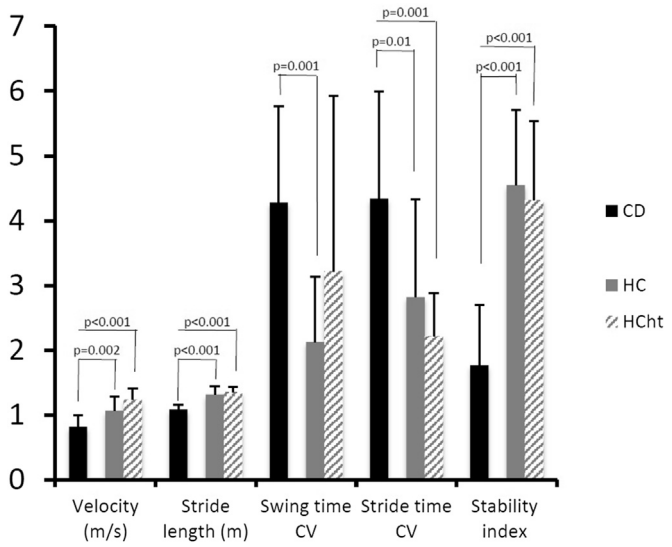

Fig. 1. Gait parameters in patients with cervical dystonia (CD), healthy controls (HC) and HC with turned head (HCht).
Figure Legend: p values for groups comparison with Kruskal-Wallis test: velocity ($p < 0.001$); stride length ($p < 0.001$); stride time CV ($p = 0.002$); swing time CV ($p = 0.009$); stability index ($p < 0.001$). Columns and bars show median values + standard error.

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Author contributions

Marcello Esposito: conception and organization of the study; writing, review and critique of the manuscript.

Raffaele Dubbioso: conception and execution of statistical analysis; review and critique of the manuscript.

Silvio Peluso: organization and execution of the study; execution of statistical analysis; review and critique of the manuscript.

Antonio Picone: organization and execution of the study; review and critique of the manuscript.

Bruno Corrado: organization and execution of the study; review and critique of the manuscript.

Clemente Servodio Iammarone: organization and execution of the study; review and critique of the manuscript.

Roberto Allocca: organization and execution of the study;

manuscript review and critique.

Fiore Manganelli: organization and execution of the study; review and critique of the manuscript; Lucio Santoro: conception of statistical analysis, review and critique of the manuscript.

Alfonso Fasano: Conception of the study, execution of statistical analysis, review and critique of the manuscript.

Author disclosures

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2017.07.005.

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