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BRIEF COMMUNICATION

The occurrence of lateral shift in cervical dystonia

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Abstract Aim of this study is to identify factors contributing the occurrence of neck lateral shift (LS) in patients with cervical dystonia (CD). A retrospective analysis focused on the treatment with botulinum toxin (BTX) was conducted on 38 consecutive idiopathic CD patients comparing subjects with and without LS. The main result was the evidence of a significantly higher BTX inter-side dose difference in patients with LS suggesting that this uncommon phenotype may be an artifact of chronic therapy with BTX.

Keywords Cervical dystonia · Botulinum toxin · Lateral shift

Abbreviations

LS	Lateral shift
CD	Cervical dystonia
BTX	Botulinum toxin

Introduction

Cervical dystonia (CD) is a focal dystonia of neck muscles that produces abnormal neck postures over the trunk and/or of the head over the neck. CD presents with many different clinical features depending on the main position of the head and neck with rotation and tilt to the shoulders in most of the cases [1]. The lateral shift (LS) is a form of CD where the head moves laterally from the midline and the base of the neck is parallel to the base of the head (Fig. 1). Based on Reichel's description of CD phenomenology, LS is the result of a combination between laterocollis and contralateral laterocaput [2]. LS is an uncommon phenotype compared to laterocollis and torticollis and it is considered a rather unusual presentation at the onset of CD; sagittal shift seems also to be an uncommon phenotype and it is often associated to neurodegenerative disease [3]. Clinical course of idiopathic CD often shows changes of the abnormal posture of the neck and head over time, possibly due to either a spontaneous evolution of dystonia or the effect of botulinum toxin (BTX) treatment [4]. Nevertheless, LS may be a different form of CD and therefore we sought to identify the factors contributing to its occurrence. For this purpose, we conducted a study comparing the clinical and BTX treatment features of idiopathic CD patients with and without LS.

Methods

Study design

This is a retrospective study including consecutive patients with idiopathic isolated CD under treatment with BTX at the Department of Neuroscience, Reproductive Sciences, and Dentistry of Federico II University of Naples from 2009 to 2015. Because of the difficulty of converting units of BTX from one brand to another, as different brands are considered not equivalent [5], we included only patients treated with the same brand to allow a more reliable group comparison of the amount of BTX between different injections. As the most used toxin in our center [6] for CD is abobotulinum toxin A (abo-BTXA, Dysport™, Ipsen) in

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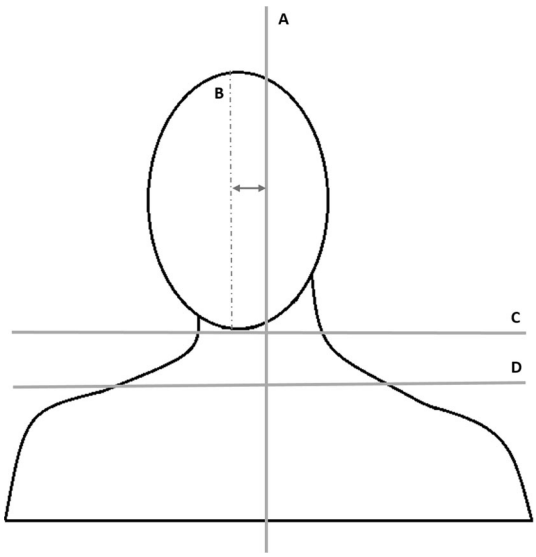

Fig. 1 Lateral shift phenotype: **a** *midline* of the trunk; **b** *midline* of the head; **c** axial plane running through the *base* of the head; **d** axial plane running through the *base* of the neck. *Arrows* show the lateral shift of the head from the *midline*

this study, we considered only patients treated with abo-BTX A. Idiopathic isolated forms of dystonia were diagnosed according to the more recent classification [7]; all cases with a possible secondary origin of CD were excluded. Demographic and clinical data of all patients were collected: age, sex, disease duration, CD phenotype, evidence of LS, time at LS onset, and clinical severity measured with the Tsui scale [8]. According to the presence of LS, patients were divided in two groups, with LS (LS group) and without LS (nLS group). Details of BTX treatment were collected as following: duration of treatment for both groups, duration of treatment preceding the occurrence of LS in the LS group, average total amount of BTX and the mean difference of dose injected between right and left cervical muscles (inter-side dose difference, IDD) of the last four treatments for the nLS group and of the last four treatments preceding the occurrence of LS for the LS group. BTX was injected in one or more of following muscles: sternocleidomastoid (SCM), trapezius (TPZ), splenius capitis (SC), levator scapulae (LevS). In both group, the rate of injection (RI) was calculated for each cervical muscle as the ratio between the number of patients of one group injected in that muscle and the total number of patient of the same group. Demographic, clinical, and pharmacological data were compared between the two groups with statistical procedure.

Statistical analysis

For inter-group comparison (LS versus nLS patients), Mann–Whitney U-test was performed for non-parametric variables and independent samples *t* test for parametric variables. Chi-square test was used to compare gender distribution, medication, and CD phenotypes between two groups. Data were analyzed using software (SPSS v. 19.0 for Windows; SPSS Inc.).

Results

Data of 38 consecutive patients were collected. 11 of them presented LS (torticollis in 4 cases and laterocollis in 7) while the remaining 27 patients had no evidence of LS (torticollis in 8 cases, laterocollis in 13, retrocollis in 4, and antecollis in 2). Demographic data, duration of disease, and the mean Tsui score were comparable between the two groups. None of the patients of the LS group presented neck shift at CD onset. The whole BTX treatment duration was not different between the two groups. As for the dose of BTX given in the last four injections in the nLS group and in the last four injections before the LS occurrence in the LS group, the mean total amount was comparable between the two groups while the IDD value of LS group was significantly higher. The RI of cervical muscles showed that the most injected muscles were SCM and SC in both group. All results of the study are summarized in Table 1.

Discussion

Cervical dystonia shows various phenotypes related to the main neck deviation. Idiopathic isolated CD, previously known as primary CD, presents as a combination of laterocollis and torticollis most of the times, other forms like antecollis and retrocollis are less frequent. The treatment with BTX is proved to be effective in reducing abnormal deviation of neck and pain in CD, and few studies confirmed efficacy and safety of the treatment over time [9]. During the disease course, CD phenotype may show some changes that are usually minimal, and especially BTX can partly correct cervical abnormal position [10]. From this study, LS seems to be a clinical feature of CD not present at the onset and developed during the years. The only significant difference between patients with LS and the nLS group is the IDD. This result would suggest that LS may be produced by an imbalance of cervical muscle strength between the right and left side related to excessive difference of BTX dose between the two sides. On this base, LS should be more frequent when sustained muscle contraction is prevailing on one side of the neck like in laterocollis and torticollis that are indeed the only phenotypes associated to LS in this study. Actually these types of CD were also very frequent in nLS group where neck

Table 1 Demographic and clinical features of patients with (LS) and without lateral shift (nLS)

	LS ($n = 11$)	nLS ($n = 27$)	p values
Age, years ± SE	60.5 ± 3.7	59.9 ± 2.9	0.9
Gender, M/F	6/5	12/15	0.2
Disease duration, years ± SE	10.7 ± 2.1	12.2 ± 1.8	0.6
Tsui rating scale	7.2 ± 0.8	7.8 ± 0.6	0.6
Duration of treatment, years ± SE (total)	7 ± 0.9	6.2 ± 0.9	0.5
Duration of treatment, years ± SE (before LS)	4.6 ± 0.7	NA	
BTX dose, I.U. ± 1 SE	411.4 ± 29.5	351.4 ± 15.9	0.1
IDD, I.U. ± 1 SE	192 ± 17.4	87.3 ± 17.9	<0.001
CD phenotypes, ratio (%)			
Torticollis	4/11(36.4)	8/27(29.6)	0.3
Laterocollis	7/11(63.6)	13/27(48.1)	0.2
Retrocollis	0/11(0)	4/27(14.8)	0.2
Anterocollis	0/11(0)	2/27 (7.4)	0.5
BTX injection, ratio (%)			
SCM	10/11(90.9)	25/27(92.6)	0.5
LevS	4/11(36.4)	9/27(33.3)	0.3
SC	7/11(63.6)	23/27(85.2)	0.1
TPZ	4/11(36.4)	12/27(44.4)	0.3

LS lateral shift, *M* male, *F* female, *SE* standard error, *CD* cervical dystonia, *BTX* botulinum toxin, *SCM* sternocleoidomastoid muscle, *TPZ* trapezius muscle, *LevS* levator scapulae muscle, *SC* splenius capitis muscle, *I.U.* international unit, *IDD* inter-side dose difference, *NA* not applicable

deviation, although with major evidence on one side, could result from bilateral muscle activation and BTX would be therefore injected with a relatively smaller IDD. Most frequently injected muscles in LS group were SCM and SC and these are the most injected also nLS patients thus there would be in no association with specific injected muscles and neck shift. Then, LS would not origin from a special type of CD and the main factor leading to LS may be the asymmetry of cervical muscle activation that can be revealed at clinical examination or with the aid of electromyography. The length of disease and duration of the treatment seem not to contribute significantly on the LS occurrence. In our group of patients, LS usually occurs after few years of periodic BTX injections and then it can be considered a cumulative effect of treatment with BTX in CD patients with prevalent affection of one side. Botulinum neurotoxins are not interchangeable [5] thus we chose to limit our observation to only patients treated with the same brand to have a convincing comparison of the BTX amount injected in each patient. Despite this study is only about abo-BTX A, it is reasonable to assume that an excessive IDD of other licensed formulations can similarly produce LS in patients treated with those toxins.

We can speculate that BTX withdrawal could reduce LS but, at the same time, dystonic symptoms like spasms and pain would get worse and would be poorly tolerated. In our LS cohort, only one patient accepted to interrupt BTX injection for six months having a considerable reduction of neck shift (pictures of this patient are presented in Fig. 2). Despite the introduction of trihexyphenidyl and clonazepam, patient reported a worsening of dystonia and the treatment with BTX was resumed. Therefore, to correct the neck shift, we would suggest to reduce the IDD and the total amount of BTX injected rather to stop BTX treatment.

Torticollis and laterocollis cause an abnormal deviation of the neck that, however, reflect a physiological position of cervical spine since tilting and rotation of head and neck are normal movements. The shift of the neck is instead a condition that is never present in healthy subjects as it does not produce a physiological movement. This consideration may suggest that LS could be a phenotype with a higher risk of complication in CD, especially related to spine deformities [11], according to a more pathological position of neck compared to other CD phenotypes. Actually, bilateral globus pallidus internus deep brain stimulation for the treatment of CD is reported to produce only poor improvement in patients presenting LS [12].

In conclusion, LS seems not to be a phenotype occurring at CD onset and it could develop over time because of recurrent injections of BTX in cervical muscles. LS would then represent a sign of chronic use of botulinum neurotoxins and not properly an adverse event related to treatment. This study was limited by a retrospective methodology and a relatively small number of patients, our interpretation of LS pathophysiology should be confirmed in next prospective studies with larger samples of patients

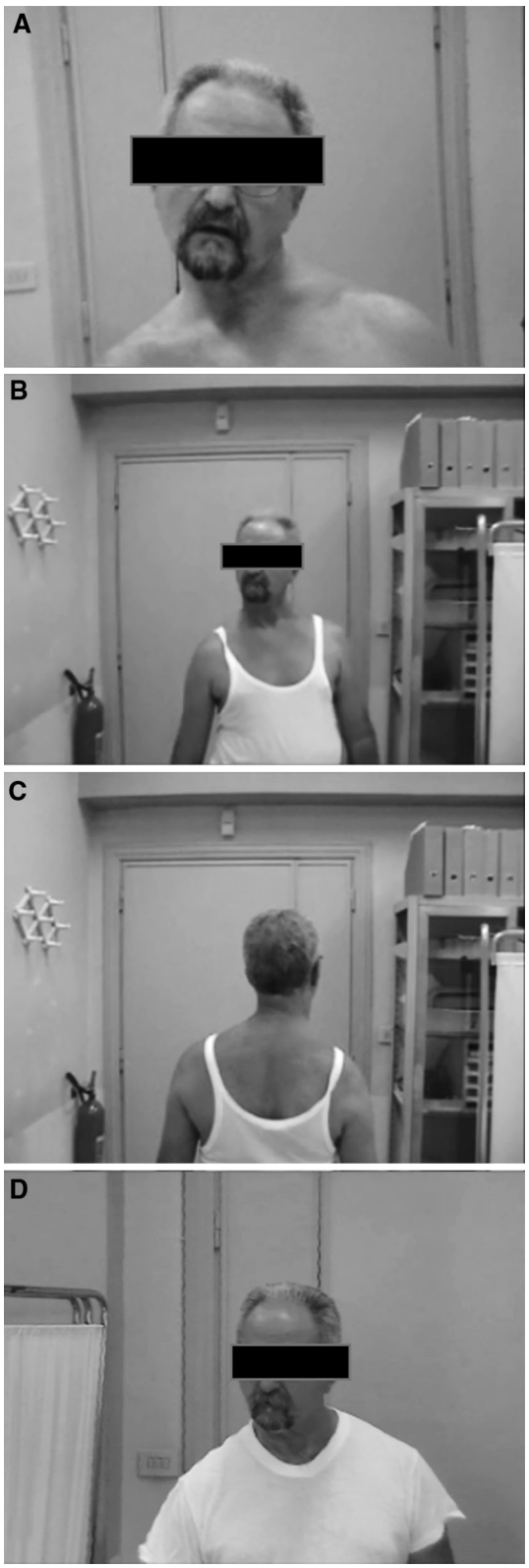

Fig. 2 The effect of botulinum toxin suspension on lateral shift (LS): **a** laterocollis before LS; **b** LS occurrence (*front side*); **c** LS occurrence (*back side*); **d** reduction of neck shift after suspension of botulinum toxin injections

with idiopathic isolated CD. The evidence of LS may indicate that the amount of BTX injected could be excessive in one side of the neck and clinicians should be aware of that to plan a safe and helpful treatment of dystonia, avoiding performing consecutive injections with a large difference of dose between sides for a long time.

Compliance with ethical standards

Conflict of interest The authors do not have financial disclosures or conflict of interest concerning the research related to the manuscript.

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