Marciniec Michał, Szczepańska-Szerej Anna, Rejdak Konrad. Cervical dystonia: pain relieving effects of botulinum toxin treatment. Journal of Education, Health and Sport. 2018;8(8):147-154. eISNN 2391-8306. DOI
http://dx.doi.org/10.5281/zenodo.1302493
http://ojs.ukw.edu.pl/index.php/johs/article/view/5617

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 05.06.2018. Revised: 28.06.2018. Accepted: 01.07.2018.

Cervical dystonia: pain relieving effects of botulinum toxin treatment

Michał Marciniec[1], Anna Szczepańska-Szerej[1], Konrad Rejdak[1]

[1]Chair and Department of Neurology, Medical University of Lublin, Poland

* E-mail address: lekmarciniec@gmail.com

ABSTRACT

Cervical dystonia (CD) is a third most common movement disorder characterized by sustained or intermittent muscle contractions causing abnormal movements and postures of head and neck. Physical, emotional, cognitive, and self-awareness aspects are also affected, so CD is currently considered to be a “network” disorder with the involvement of multiple brain regions and cellular mechanisms. Pain occurs in 54.6% to 88.9% of patients with CD and is the most disabling non-motor symptom which strongly attributes to the quality of life deterioration. The dystonia-related pain is also the main reason patients are looking for treatment. Despite the high prevalence only small number of studies develops this issue. Botulinum toxin (BoNT) is a safe, efficacious and first choice treatment for CD. Up to 90% of patients reports an improvement in pain and motor symptoms after BoNT injections, however above mentioned effects may be partially independent due to the earlier and longer pain relief compared to muscle relaxation. The results of current studies suggest analgesic effects of BoNT are related to not only the acting in the neuromuscular junction. The central processing of nociceptive stimuli is contributed to be the main effect of BoNT analgesic therapy. To date, evidence for the association between dystonia-related pain and BoNT treatment become more significant but is still lacking. Further research is needed to investigate above correlation and issue an unambiguous high-level recommendations of analgesic therapy in CD.

***Keywords*:**
Cervical Dystonia, Torticollis, Pain, Botulinum Toxins.

GLOSSARY

aboBoNT-A – abobotulinumtoxinA, **AEs** – adverse effects, **BoNT** – botulinum neurotoxin, **CD** – cervical dystonia, **DBS** – deep brain stimulation, **EMG** – electromyography, **incoBoNT-A** – incobotulinumtoxinA, **onaBoNT-A** – onabotulinumtoxinA, **PNRS** – pain numeric rating scale, **RCTs** – randomized controlled trials, **rimaBoNT-B** – rimabotulinumtoxinB, **TWSTRS** – Toronto Western Spasmodic Torticollis Rating Scale, **VAS** – visual analog scale.

INTRODUCTION

Cervical dystonia (CD) is a condition belongs to the group of hyperkinetic movement disorders with movements and postures limited to the neck and head region. CD affects from 57 per million people in Europe to as high as 280 per million people in the USA, thereby is the third most common movement disorder (after Parkinson's disease and essential tremor). The onset of CD typically takes place in fifth decade [1].

CD is not only the sensorimotor disease. Physical, emotional, cognitive, and self-awareness aspects are also affected. The heterogeneity of motor and non-motor symptoms, possible pathophysiological changes and various categorization support the assertion that CD is a "network" disorder with multiple brain regions and cellular mechanisms involvement [2]. Self-perceived non-motor aspects like sleep, fatigue, mood, and cognitive processing are strongly related to the disability, however the most common cause of disability remains the pain which is associated with such psychological aspects as depression and anxiety [3].

Definition of the dystonia

An expert consensus defined dystonia "as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal movements, postures, or both" [4]. Above mentioned movements and postures are usually repetitive, stereotyped, predictable and involve usually the same part of the body. The muscle contractions in the course of dystonia are involuntary, however voluntary action exacerbate muscle activation [5].

Clinical examination has a crucial role in the identification of the disease and there are no specific diagnostic test used to confirm the diagnosis. Generally, neurophysiological tests are not routinely recommended for diagnosis and classification of dystonia in the most of global available guidelines, however electromyography (EMG) may be useful. Similarly, brain imaging is not necessary to confirm the diagnosis of dystonia, although is proposed for screening of secondary forms of dystonia [6].

CD as a type of dystonia

CD is the most common form of focal dystonia. The lateral tilting (laterocollis) and turning (torticollis) of the head are typical clinical manifestations of CD [5]. The full nomenclature refers to the CD include:

1) torticollis, laterocollis, anterocollis and retrocollis caused by the muscles operating on cervical spine, represent 20% of the CD cases
2) torticaput, laterocaput and anterocaput, where muscles acting on the basis of skull and atlanto-occipital joints, represent similarly 20% of the CD cases [5,7].

Both above mentioned types occur at the same time in about 60% patients with CD. The main difference between torticollis and torticaput is the rotation angle of the skull and three upper vertebrae (C1, C2, C3). Torticollis refers to the same rotation angles between each four above mentioned levels as opposite to torticaput, in which the skull and C1 have the same and C2 and C3 have different rotation angles. Clinical examination is the most important in distinguishing between these two types of CD, however the imaging techniques such as CT

scans may be useful. Observation of the angle between the base of the skull, cervical and thoracic spine is sufficient for clinical differentiation between antero/retrocaput and antero/retrocollis. The correct classification of CD based on above criteria helps to avoid botulinum toxin (BoNT) injections into muscles not participating in the pathogenesis of the disease [7].

Changes in the central nervous system

There is a growing evidence that the fundamental issue in the course of CD is abnormal neural control of neck muscles. Currently available studies reported the brain abnormalities of the cerebral cortex, cerebellum, or vestibular pathways [8]. The direct association between involved muscles and brain activity was examined in the study with the use of resting state functional MRI. Reduced connectivity was observed within a distributed network including the premotor cortex, supplementary motor area, primary sensorimotor cortex, and secondary somatosensory cortex compared to healthy controls. There were also brain regions with increased connectivity: the prefrontal and parietal cortex and the network of executive control. Interestingly, the administration of BoNT, which is the first-line treatment for CD, resulted in partial restoration of above neuronal networks some weeks after the injections [9].

Unfortunately, the precise assessment of brain activity in the course of CD is hindered by the moving of the head which impairs fMRI reading. Following current models, CD shall be considered to be a network disorder involving several brain regions, although how the network is disrupted remains uncertain [8].

Botulinum toxin as a first-line treatment for CD

Currently available options for CD treatment are BoNT, neurosurgery (DBS, deep brain stimulation) and physical therapy. Oral medications like anticholinergics are not usually used due to the significantly lower effectiveness compared to BoNT, which is a first-line therapy in CD treatment [10]. BoNT is also used in the treatment for movement disorders like focal dystonias (CD, blepharospasm, oromandibular dystonia, limb dystonias), hemi-facial spasm, tremors, tics as well as motor symptoms of Parkinson's disease. The beneficial effect of single BoNT injection lasts for around three months thereby treatment must be repeated periodically [11]. The guidelines on diagnosis and treatment for dystonias of European Federation of Neurological Societies recommended BoNT treatment as a safe, efficacious, first choice treatment for CD even when repeated treatments are performed over many years [12].

There are two types of BoNT used in clinical practice with similar efficacy – type A and B. Following recommendation of American Academy of Neurology, four types of BoNT may be used in CD treatment with following strength of recommendations:

- level A: abobotulinumtoxinA (AboBoNT-A) and rimabotulinumtoxinB (rimaBoNT-B), which are established as effective and should be offered,
- level B: onabotulinumtoxinA (onaBoNT-A) and incobotulinumtoxinA (incoBoNT-A), which are probably effective and should be considered [13].

Scales used in clinical studies and clinical practice

Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and the Tsui score are the most commonly used scales in the clinical studies. TWSTRS is divided into 3 parts for assessing the severity, disability and pain in the course of CD:

1) severity subscale: maximum 35 points for the assessment of maximal excursion (rotation, tilt, anterocollis or retrocollis, lateral shift, sagittal shift), duration factor, effect of sensory tricks, shoulder elevation or anterior displacement, range of motion and time of ability to maintain the head within neutral position without the use of sensory tricks,
2) disability subscale: maximum 35 points for the assessment of the ability to perform particular daily activities,
3) pain subscale: maximum 20 points for the assessment of the severity, duration and disability due to pain [14].

The Tsui scale is another scale used to evaluate CD symptoms. This scale includes less parameters compared to TWSTRS and due to its simplicity may be used in clinical routine provide quick evaluation. The parameters absent in Tsui score and present in TWSTRS are: effect of sensory tricks, disability subscale and pain subscale. Unfortunately, neither of scales separate "collis" from "caput" disorders present in the most current classification of CD. The comparison of above scales are presented in Table 1 [15].

Table 1. The similarities and differences between TWSTRS (Toronto Western Spasmodic Torticollis Rating Scale) and Tsui score [15].

	Similarities		**Differences**		
	TWSTRS	**Tsui**	**TWSTRS**	**Tsui**	
Duration factor	Yes	Yes	Yes	Yes	Disability scale
Rating for amplitude of movements	Yes	Yes	Yes	No	Pain scale
Rating for shoulder elevation	Yes	Yes	No	Yes	Simplicity and easy to apply
"Collis" and "caput" as separated types of CD	No	No	Yes	No	Rating for shift
			No	Yes	Rating for tremor
			Yes	No	Effect of sensory tricks
			Yes	No	Standardized videotape protocol

PAIN AS A COMMON SYMPTOM OF CD

The role of pain in CD pathophysiology and severity has not been fully elucidated [16]. The prevalence of pain varies from 54.6% to 88.9% of patients with CD, however, despite the high prevalence, only small number of studies develops this issue.

Dystonia-associated pain is the most common and disabling non-motor symptom which strongly attributes to the quality of life deterioration [17]. Pain is also the main reason patients are looking for treatment [10]. Interestingly, the results of the observational studies suggest that there are some geographic differences in pain perception: US patients report higher levels of pain than patients from Europe or rest of world in TWSTRS pain subscale without difference in ratings of disability, thereby the difference may be related to the perception only [18].

Scales used in pain evaluation

There are three the most frequently used scales in the evaluation of pain in the course of CD. The simplest is the 11-point pain numeric rating scale (PNRS), which origins from visual analog scale (VAS). A whole number from the range of 0 to 10 indicated by patient correlate with pain severity, where 0 representing one pain extreme ("no pain") and 10 representing the other extreme ("worst pain imaginable") [19]. Second example of pain evaluation is the pain subscale of TWSTRS mentioned above. Third scale commonly used in clinical studies is The Cervical Dystonia Impact Profile (CDIP-58) which includes 8 subscales for the assessment of head and neck symptoms, pain and discomfort, upper limb activities, walking, sleep, annoyance, mood, and psychosocial functioning (high scores indicate worse health) [20]. Pain scales were found to correlate with one another [16].

Pathophysiology of pain

Due to the formerly accepted fact pain occurs as a consequence of sustained muscle contraction, pain assessment was not specifically targeted in studies for a long time. Currently there is a growing evidence that pain level may correlate with the degree of muscle tension and head deviation, however not all the patients with similar degrees of dystonia experiences equal amounts of pain. Furthermore, the objective severity of neurologic signs usually do not correlate with the severity of muscle tension and head deviation [10].

There are two theories explaining the origin of the pain. The first one assume that constant and prolonged afferent input due to the muscle contraction damages central processing of nociceptive stimuli at the spinal level and reduces the threshold for experiencing pain. The second one explains that the pain sensation may be generated in basal ganglia nuclei as a result of the dysfunction of the neurotransmission systems [17].

The serotonergic signaling alterations in various brain areas may be related to both motor and non-motor symptoms in CD. One of the most recent study on the non-displaceable binding potential (BPND) of presynaptic serotonin transporter with the use of positron emission tomography revealed that higher BPND in the dorsal raphe nucleus was statistically significantly correlated with pain (rs, Spearman's rank correlation = 0.73, $p < 0.001$) as well as motor symptom severity and sleep disturbances [21].

Mechanisms of analgesic activity of botulinum toxin

Inhibiting the release of acetylcholine at the neuromuscular junction is the major but not the only mechanism of BoNT acting. The direct mechanism of pain in CD remains unknown, similarly to the analgesic activity of BoNT. Currently available studies support a thesis that pain may not be the only consequence of muscle hyperactivity [22]. Pain relief related to the BoNT injection (measured in VAS scale) appears before muscle relaxation (measured in TWSTRS motor score) and that effect lasts longer than the effect on motor

improvement. Interestingly, after peripheral injection, the enzymatic activity of BoNT/A was detected in motor and sensory regions of the brainstem and spinal cord. Although the BoNT/A presence in motor regions remains unexplained, authors of the study associated the BoNT/A presence in sensory regions with antinociceptive activity [23]. Summarizing, more and more data suggest that analgesic effects of BoNT could be attributed to the direct action in central nervous system [10,22].

Botulinum toxin in clinical studies on cervical dystonia-associated pain relief

Up to 90% of patients reports an improvement in pain and dystonic symptoms after BoNT injection with the similiar results of BoNT-A and BoNT-B [24]. In one of the review articles included five randomized controlled trials (RCT), the use of ona- and abo-BoNT-A reduced pain in 71% of the patients compared to 12% with placebo group ($p < 0.00001$). The authors summarize that there are grounds for recommending BoNT-A in cervical dystonia-related pain treatment (class I evidence, level A). In other two RCTs BoNT-A and BoNT-B have comparable effects on the reduction of TWSTRS pain subscale [25].

In the largest to date observational study enrolled 1.037 patients with CD at 88 sites in the United States, participants were divided into two groups of pain severity: no/mild pain (PNRS score 0–3) and moderate/severe pain (PNRS score 4–10). The results revealed that 88.9% of patients reported pain related to CD at baseline. Moderate or severe pain at baseline occurred in 70.7% of them and in 29.3% pain was mild or absent. No or mild pain more likely to occured in older patients (60.9 vs. 56.8 years, $p<0.0001$) with higher levels of education ($p = 0.0005$). Conversely, moderate/severe pain were observed in patients with higher score in the TWSTRS subscales of severity (17.7 vs. 16.2, $p < 0.0001$) and disability (12.7 vs. 7.5, $p < 0.0001$) as well as in patients received higher mean dose of onabotulinumtoxinA (177.3 vs. 158.0 U, $p = 0.0001$) injected in more muscles (4.1 vs. 3.7, $p < 0.0001$) and reported significantly higher usage of analgesics, antianxiety agents, and antidepressants [16].

Smaller class I studies with the use of serotypes of A and B toxins report similar effect on the magnitude of pain relief. The subjects being still of investigation are whether different forms of BoNT or higher doses are more effective in relieving the CD-associated neck pain [26].

CONCLUSIONS

The results of available studies suggest that cervical dystonia-related pain is one of the most frequent symptoms, represents an important cause of disability and deteriorates quality of life to a large extent. The administration of BoNT reduces pain in the mechanism partially independent of the muscle relaxation and there is a growing evidence that central processing of nociceptive stimuli could be the main antinociceptive mechanism. To date, evidence for the association between BoNT treatment and non-motor symptoms of CD become more significant but is still lacking. Further research is needed to investigate above correlation and issue an unambiguous high-level recommendations.

References

[1] Castelão M, Marques RE, Duarte GS, Rodrigues FB, Ferreira J, Sampaio C, Moore AP, Costa J. Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database Syst Rev*. 2017;12. https://doi.org/10.1002/14651858.CD003633.pub3.
[2] Schirinzi T, Sciamanna G, Mercuri NB, Pisani A. Dystonia as a network disorder: a concept in evolution. *Curr Opin Neurol*. 2018; https://doi.org/10.1097/WCO.0000000000000580.

[3] Isabel Useros-Olmo A, Martínez-Pernía D, Huepe D. The effects of a relaxation program featuring aquatic therapy and autogenic training among people with cervical dystonia (a pilot study). *Physiother Theory Pract*. 2018;25:1-10.
[4] Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, et. al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord*. 2013;28(7):863-73.
[5] De Pablo-Fernandez E, Warner TT. Dystonia. *Br Med Bull*. 2017;123(1):91-102.
[6] Tamás G, Abrantes C, Valadas A, Radics P, Albanese A, Tijssen MAJ, et al. Quality and reporting of guidelines on the diagnosis and management of dystonia. *Eur J Neurol*. 2018;25(2):275-283.
[7] Reichel G. Cervical dystonia: a new phenomenological classification for botulinum toxin therapy. *Basal Ganglia.* 2011;1:5-12.
[8] Prudente CN, Stilla R, Singh S, Buetefisch C, Evatt M, Factor SA, et al. A functional magnetic resonance imaging study of head movements in cervical dystonia. *Front Neurol*. 2016;7:201.
[9] Delnooz CCS, Pasman JW, Beckmann CF, van de Warrenburg BPC. Task-Free Functional MRI in Cervical Dystonia Reveals Multi-Network Changes That Partially Normalize with Botulinum Toxin. *PloS one.* 2013;8:e62877.
[10] Novak I, Campbell L, Boyce M, Fung VS. Botulinum toxin assessment, intervention and aftercare for cervical dystonia and other causes of hypertonia of the neck: international consensus statement. *Eur J Neurol*. 2010;2:94-108.
[11] Tater P, Pandey S. Botulinum toxin in movement disorders. *Neurol India*. 2018;66:S79-S89.
[12] Albanese A, Asmus F, Bhatia KP, Elia AE, Elibol B, Filippini G, Gasser T, Krauss JK, Nardocci N, Newton A, Valls-Solé J. EFNS guidelines on diagnosis and treatment of primary dystonias. *Eur J Neurol*. 2011;18(1):5-18.
[13] Simpson DM, Hallett M, Ashman EJ, Comella CL, Green MW, Gronseth GS, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2016;86: 1818-26.
[14] Jost WH, Hefter H, Stenner A, Reichel G. Rating scales for cervical dystonia: a critical evaluation of tools for outcome assessment of botulinum toxin therapy. *J Neural Transm*. 2013;120(3):487-96.
[15] Jost WH, Hefter H, Stenner A, Reichel G. Rating scales for cervical dystonia: a critical evaluation of tools for outcome assessment of botulinum toxin therapy. *J Neural Transm.* 2013;120:487–96.
[16] Charles PD, Adler CH, Stacy M, Comella C, Jankovic J, Manack, et al. Cervical dystonia and pain: characteristics and treatment patterns from CD PROBE (Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy). *J Neurol*. 2014;261(7):1309-19.
[17] Avenali M, De Icco R, Tinazzi M, Defazio G, Tronconi L, Sandrini G, et al. Pain in focal dystonias - A focused review to address an important component of the disease. *Parkinsonism Relat Disord*. 2018. https://doi.org/10.1016/j.parkreldis.2018.04.030.
[18] Trosch R, Misra P, Maisonobe P, Om S. Geographic Differences in Pain Perception in Patients with Cervical Dystonia (P1.033). *Neurology.* 2016;86:1-33.
[19] Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res*. 2011;11:S240-52.

[20] Cano SJ, Hobart JC, Edwards M, Fitzpatrick R, Bhatia K, Thompson AJ, et al. CDIP-58 can measure the impact of botulinum toxin treatment in cervical dystonia. *Neurology*. 2006;67(12):2230-2.
[21] Smit M, Vállez García D, de Jong BM, Zoons E, Booij J, et al. Relationships between Serotonin Transporter Binding in the Raphe Nuclei, Basal Ganglia, and Hippocampus with Clinical Symptoms in Cervical Dystonia: A [11C]DASB Positron Emission Tomography Study. *Front Neurol.* 2018;28(9):88.
[22] Relja M, Miletić V. When movement disorders hurt: Addressing pain in hyperkinetic disorders. *Parkinsonism Relat Disord*. 2017;44:110-113.
[23] Matak I, Lacković Z, Relja M. Botulinum toxin type A in motor nervous system: unexplained observations and new challenges. *J Neural Transm*. 2016;123(12):1415-21.
[24] Camargo CH, Cattai L, Teive HA. Pain Relief in Cervical Dystonia with Botulinum Toxin Treatment. *Toxins (Basel)*. 2015;7(6):2321-35.
[25] Contarino MF, Van Den Dool J, Balash Y, Bhatia K, Giladi N, et al. Clinical Practice: Evidence-Based Recommendations for the Treatment of Cervical Dystonia with Botulinum Toxin. *Front Neurol*. 2017;8:35.
[26] Safarpour Y, Jabbari B. Botulinum Toxin Treatment of Movement Disorders. *Curr Treat Options Neurol*. 2018;20(2):4.