Parkinsonism and Related Disorders 65 (2019) 252–255

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

Pain in cervical dystonia: Evidence of abnormal inhibitory control

Michele Tinazzi[a,1], Giovanna Maddalena Squintani[b,1], Kailash P. Bhatia[c], Alessia Segatti[b], Francesco Donato[d], Massimiliano Valeriani[e], Roberto Erro[f,*]

[a] Department of Neuroscience, Biomedicine and Movement Science, University of Verona, Verona, Italy
[b] Neurology Unit, Department of Neuroscience, AOUI Verona, Verona, Italy
[c] Department of Clinical and Movement Neurosciences, Institute of Neurology, University College London, London, UK
[d] Department of Neurology, SS Giovanni e Paolo Hospital, 30122, Venice, Italy
[e] Neurology Unit, Ospedale Pediatrico Bambino Gesú, Rome, Italy
[f] Center for Neurodegenerative Diseases (CEMAND), Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", Universitá di Salerno, Baronissi, SA, Italy

ARTICLE INFO

Keywords:
Diffuse noxious inhibitory control
Laser evoked potentials
Dystonia

ABSTRACT

Introduction: Several observations would suggest that dystonic pain is not simply muscular in origin. While ascending nociceptive pathways are normal in cervical dystonia, it is unknown whether descending inhibitory pain pathways are also normal.

Methods: We applied a conditioned pain modulation protocol and concomitantly recorded laser evoked potentials in patients with cervical dystonia (n = 15), blepharospasm (n = 15) and healthy volunteers (n = 15).

Results: During the application of a heterotopic noxious conditioning stimulation, patients with cervical dystonia, but not with blepharospasm, lacked the physiological reduction of the perceived intensity of a painful test stimulus as well as of the related evoked potential. This was observed in cervical dystonia patients regardless of the presence of clinical pain.

Conclusions: Our results suggest that pain in CD is not simply muscular in origin but it also possibly reflects a dysfunction of the descending pain inhibitory control, thus providing a novel venue to explore the pathophysiology of pain in CD.

1. Introduction

Pain is the most common and disabling non-motor symptom in cervical dystonia (CD), usually reported in the neck and shoulder muscles by up to 75% of patients [1], which is a much higher rate compared to other forms of focal dystonia such as blepharospasm (BPS) [1–3].

It might be speculated that pain in CD is not of muscular origin alone, since it can occur in non-dystonic cervical muscles and does not clearly correlate with the degree of contraction of dystonic muscles as measured with pressure algometry [4]. This is further suggested by the fact that in a proportion of CD patients pain is not relieved following botulinum neurotoxin (BoNT) injections despite the improvement of dystonic contractions [5,6], and its improvement after deep brain stimulation (DBS) of the globus pallidus internus (GPi) is temporally dissociated from the motor outcome [7,8]. Altogether, these findings might suggest that pain in CD may also be due to an abnormal central processing of nociceptive stimuli.

We previously reported that the N2/P2 laser evoked potentials (LEPs), originating in the cingulate cortex and insula [9], are normal in CD, suggesting there is no overactivity of the ascending nociceptive pathways [10]. However, the hypothesis that descending inhibitory control might be deficient in dystonia has not yet been tested. This can be explored with a conditioned pain modulation (CPM) protocol [11], which consists in delivering a painful conditioning stimulus (CS) alongside another experimentally induced painful test stimulus (TS) [5]. According to the principle of "pain inhibits pain", a physiological reduction of the perceived TS is usually observed [11]. Alterations of CPM have been proposed as one of the underlying mechanisms contributing for the development of chronic pain conditions.

Given the high prevalence of pain in CD, we primarily sought to test the hypothesis that these patients might have an abnormal response to a CPM protocol. We further included patients with BPS to assess possible CPM differences with CD patients.

* Corresponding author.
E-mail address: rerro@unisa.it (R. Erro).
[1] contributed equally to the work.

https://doi.org/10.1016/j.parkreldis.2019.06.009
Received 27 February 2019; Received in revised form 21 May 2019; Accepted 9 June 2019

2. Methods

Forty-five subjects (15 patients with CD, 15 patients with BPS and 15 HC) participated to the study. There were no differences between groups in terms of age (CD = 55.58 ± 12.93; BPS = 62.08 ± 15.53; HC = 48.58 ± 12.68; $p > 0.05$) and sex (CD = 6 F/6 M; BPS = 8 F/4 M; HC = 4 F/8 M; chi 2 = 2.67, $p > 0.05$). Patients with CD and BPS had similar disease duration (9.08 ± 4.83 and 8.62 ± 4.72, respectively; $p > 0.05$) and disease severity as assessed with the Unified Dystonia Rating Scale [12] (CD = 4.58 ± 1.93; BPS = 4.22 ± 1.52, $p > 0.05$), and were tested 4 months after their last set of BoNT injections. Eight out of 15 CD patients (53.3%) had clinical pain as indicated by a 11-point numerical rating scale (NRS) > 3 on a typical day, as opposed to only 1 patient with BPS (6.7%, Fisher $\chi^2 = 7.8$, $p = 0.014$). All 8 CD patients reported a moderate relief of pain following BoNT, despite a strong improvement of the abnormal posture.

Exclusion criteria were: presence of tremor to avoid artifacts during the recording; clinical and electrophysiological evidence of a peripheral neuropathy or of any other diseases potentially causing sensory impairment (i.e., diabetes.); headache or other types of pain for HC, whereas for both patient groups presence of pain in body areas far from the affected one; cognitive impairment (MMSE < 26); depression [Beck depression inventory (BDI) ≥14] and anxiety [Beck anxiety inventory (BAI) ≥16]; and current use of anti-depressants, anxiolytic or analgesic drugs.

LEPs recording were performed as previously described [13]. In brief, TS consisted of cutaneous heat stimuli delivered by a Nd:YAP laser stimulator on the dorsum of the right hand with an intensity of stimulation which was set 2 mJ above the pain threshold and kept unchanged throughout the recording. The N2/P2 LEPs were obtained from recording electrodes placed over the scalp (Cz, Fz), with the reference electrode at the nose. LEPs were measured on averages of 25–30 trials, after which subjects were asked to rate the pain induced by the TS (pain-rating) using an 11-point Numerical Rating Scale (NRS) ranging from 0 (e.g., no pain) to 10 (e.g., most severe pain imaginable).

LEPs and pain-ratings were collected in three different sessions: 1) baseline; 2) during the application of a heterotopic noxious conditioning stimulation (HNCS); and 3) post-HNCS. During HNCS, subjects were requested to submerge their left foot distal to the ankle joint into an ice water bath at a temperature of around 0 °C [11]. The pain intensity of the CS (i.e., ice water bath), also rated by using a 11-point NRS scale, was not significantly different between groups (Table 1) and all subjects were able to tolerate the intensity of the CS for the entire HNCS session, which lasted about 5 min. The 3 experimental sessions were separated by a 15-minute interval, as previous studies using a CPM protocol concluded that the pain-suppressive effects of the CS vanish after 5–10 min (for a review see 14). The procedures were approved by the institutional ethics committee and all subjects gave their written informed consent.

2.1. Statistical analysis

Normal distribution and equal variance were checked through the Shapiro-Wilk and Barlett tests. The mean values of pain threshold, pain-rating, N2 and P2 latencies and N2/P2 amplitude were entered into separate repeated measures analyses of covariance (ANCOVA) with *Group* as the between-subject factor and *time* (Baseline vs HNCS vs post-HNCS) as the within-subject factor. As covariates, we included age, BDI and BAI scores, which are known to interact with the outcome (i.e., LEP/Pain rating). To account for baseline differences between groups, we further computed the ratio of the N2/P2 amplitude between the HNCS and baseline session, which was entered in a one-way ANCOVA model. Greenhouse Geisser correction was used when necessary to correct for nonsphericity. Post-hoc comparisons were performed using t-tests using Bonferroni correction for multiple comparisons where needed. Cohen's d was used to calculate effect sizes, with d values < 0.5, 0.5 < d < 0.8, and d > 0.8 indicating a small, medium, and large effect respectively. Correlations between the gathered variables were performed using the Pearson's test; a 5% level of significance was used for all tests. Secondary analyses were performed to explore LEP recording and pain-rating differences between CD with and without clinical pain. All test were performed with Stata v.11.0 (Stata Corp, USA).

3. Results

No baseline differences were observed between groups in terms of LEP latency, amplitude, and pain-rating values (Table 1). As for the N2/P2 amplitude, there was a significant effect of *time* [$F_{(2,42)} = 49.97$; $p < 0.001$] and a significant *group* × *time* interaction [$F_{(2,42)} = 7.54$; $p < 0.001$]. These effects were driven by significantly higher N2/P2 amplitude during the HNCS session in patients with CD as compared to both HC ($p = 0.019$) and BPS ($p = 0.024$) (Fig. 1A), whereas no differences were found at post-HNCS (Fig. 1A; Table 1). Cohen's d using CD and HC values during the HNCS was 3.34, thus indicating a very large effect size. Analogously, the one-way ANCOVA model showed significant differences in the $N2/P2_{RATIO}$ between groups [$F_{(2,42)} = 16.76$; $p < 0.001$], with a higher ratio (indicating less N2/P2

Table 1
Summary of the electrophysiologic and psycophysical variables in Cervical Dystonia (CD), Blepharospasm (BPS) and Healthy Controls (HC).

	CD	BPS	HC	*post-hoc* p value
BASELINE				
N2 Latency (ms)	218.17 ± 12.58	220.34 ± 21.70	213.33 ± 17.29	> 0.05
P2 Latency (ms)	309.67 ± 35.03	309.25 ± 30.21	309.08 ± 34.71	> 0.05
N2/P2 Amplitude (μV)	29.76 ± 9.69	31.36 ± 8.29	29.83 ± 7.13	> 0.05
NRS_{TS}	4.58 ± 0.67	4.42 ± 0.72	4.42 ± 0.67	> 0.05
HNCS				
N2 Latency (ms)	213.83 ± 16.21	222.52 ± 16.08	223.67 ± 19.40	> 0.05
P2 Latency (ms)	299.75 ± 28.53	317.21 ± 30.91	314.33 ± 38.28	> 0.05
N2/P2 Amplitude (μV)	23.50 ± 4.84	17.72 ± 4.36	17.28 ± 5.06	0.024[a]/0.019[b]
NRS_{TS}	4.31 ± 1.24	3.30 ± 1.22	3.17 ± 0.95	0.022[a]/0.020[b]
NRS_{CS}	7.08 ± 1.93	7.00 ± 1.55	7.75 ± 2.05	> 0.05
Post-HNCS				
N2 Latency (ms)	214.92 ± 12.42	219.17 ± 19.72	212.92 ± 18.45	> 0.05
P2 Latency (ms)	313.08 ± 28.42	313.42 ± 32.60	299.78 ± 31.58	> 0.05
N2/P2 Amplitude (μV)	23.67 ± 9.68	26.68 ± 11.32	24.62 ± 8.95	> 0.05
NRS_{TS}	4.64 ± 1.09	4.58 ± 1.32	4.50 ± 0.67	> 0.05

NRS_{TS}: numerical rating scale test stimulus; NRS_{CS}: numerical rating scale conditioning stimulus. HNCS: heterotopic noxious conditioning stimulation.
[a] CD vs BPS
[b] CD vs HC.

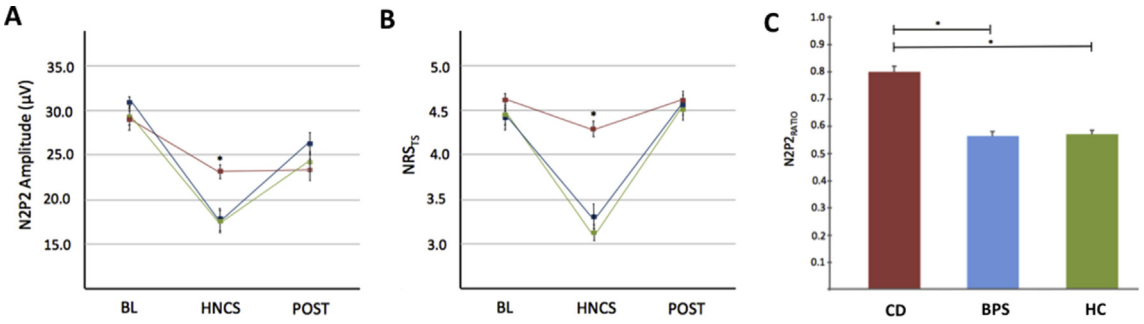

Fig. 1. Amplitude of the N2/P2 component of the laser evoked potentials (A) and pain ratings of the test stimulus (B) during the three experimental sessions in patients with cervical dystonia (CD; red squares), patients with blepharospasm (BPS; blue squares) and healthy controls (HC; green squares). C: Ratio of the N2/P2 amplitude during the application of the heterotopic noxious conditioning stimulation as compared to baseline. Data are expressed as mean ± standard error. Stars indicate statistical significance (see text for details). BL: Baseline; HNCS: heterotopic noxious conditioning stimulation; NRS_{TS}: numerical rating scale test stimulus. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

suppression) in patients with CD than in patients with BPS and HC (both $p < 0.01$; Fig. 1C).

As for the pain-rating, the repeated measure ANCOVA showed a significant effect of *time* [$F_{(2,42)} = 28.63$; $p < 0.001$] and *group* × *time* interaction [$F_{(2,42)} = 3.66$; $p < 0.01$]. These effects were driven by higher NRS during the HNCS session in patients with CD as compared to both HC and patients with BPS (both $p < 0.01$; Fig. 1B), whereas there were no differences at post-HNCS (table 1).

No significant correlations were found between psychophysical variables and LEP recording in any groups nor differences could be observed between CD patients with and without pain, both in terms of LEP recording and pain-ratings (for all comparisons $p > 0.05$; data not shown).

4. Discussion

While baseline pain rating and LEPs were normal in CD patients, confirming that there is no overactivity of the ascending pain pathways [10], we have here demonstrated that these patients have a reduced CPM response, as compared to both HC and patients with BPS, which suggests that the endogenous inhibitory pain system is primarily defective in CD.

CPM represents the human behavioral correlate of diffuse noxious inhibitory control (DNIC), initially described in rats [15]. Studies in both animals and humans have demonstrated that descending influences on spinal nociceptive processing rely on a spino-bulbo-spinal loop that crucially involves the subnucleus reticularis dorsalis (SRD) and other brainstem structures, including the periaqueductal gray and the rostral ventromedial medulla [15,16]. However, while the brainstem is critical for CPM, higher brain structures including the dorso-lateral prefrontal cortex and the middle- and posterior-cingulate cortex, modulate its expression [17]. The SDR receives somatosensory and motor cortex inputs and projects to the midline, mediodorsal, and intralaminar thalamic nuclei, a complex of about 25 thalamic nuclei that synchronize the medial and later pain systems, which in turn have strong connections with both the cingulate cortex and the striatum [17,18]. Thus, there is a strong link among these brain structures that would enhance their mutual engagement in pain-driven motor responses at both cortical, basal ganglia and brainstem levels of output.

There are no studies specifically exploring the neuroanatomical basis of pain in dystonia. Therefore, it is unclear which of these brain structures might be involved in CD and account for the CPM abnormalities observed here. Some authors have hypothesized that altered connections between basal ganglia and brainstem might account for the motor symptoms of CD [19] and this might also hold true for pain. Noteworthy, GPi DBS improves motor function and pain with a dissociated time-course [7,8]. This would suggest a complex organization of the GPi in terms of functional anatomy, with different subgroups of neurons being responsible for motor and nociceptive functions [7,8].

Whatever the precise mechanism might be, our data indicate that CPM is selectively impaired in patients with CD but not with BPS. This suggests that, although some pathophysiologic abnormalities of sensory processing might be shared across different types of dystonia [20], other mechanisms might be involved in cervical but not other forms of focal (i.e., cranial) dystonia, thus possibly accounting for the clinical differences between focal dystonia types.

It is currently unclear to what degree deficient endogenous pain modulation may be a cause or an effect of chronic pain. It might be argued, in fact, that the presence of clinical pain might have functioned as a conditioning stimulus, thus leading to a reduced CPM response. However, in our study, CPM was defective in both CD patients with and without clinical pain and no correlation was observed between CPM abnormalities and intensity of pain. This might suggest that CPM dysfunction may precede the occurrence of clinical pain in CD, but further studies are warranted to understand whether this abnormality represents on its own the functional basis of the development of overt pain in CD or acts synergistically with additional factors. Pain in CD is likely to be multifactorial, with many features, including the type (i.e., predominant phasic or tonic) and severity of dystonia, disease duration, as well as the presence of comorbid medical conditions associated with or predisposing to painful symptoms (i.e., disk herniation, joint diseases, etc.) potentially playing a role. Therefore, future ad-hoc epidemiological studies on a large sample of CD patients with and without pain assessing differences in demographic and clinical characteristics could help in identifying possible factors triggering pain.

We acknowledge the relative small sample size, which further prevented us to correlate the response to BoNT injections in terms of pain reduction and the CPM abnormality. Notwithstanding these limitations, our results suggest that pain in CD is not of muscular origin alone, but might also arise from a dysfunction of the descending pain inhibitory control, thus providing a novel venue to explore the pathophysiology of pain in CD.

Author roles

1: A) conception; B) supervision - 2: A) Acquisition of data; B) Data analysis - 3: A) writing the first draft; B) revising the draft for important intellectual content.

MT: 1A; 1B; 2B; 3A; 3B
GMS: 1B; 2A; 2B; 3B
KPB: 1B;2B; 3B
AS: 2A;2B;3B
FD: 2A;2B;3B
MV: 2A;2B;3B
RE: 1A; 1B; 2A; 2B; 3A; 3B

Full financial disclosures

RE received consultancies from Zambon, TEVA and UCB and receives royalties for the publication of “Case series in movement disorders – Common and uncommon presentations” (Cambridge University Press, 2017). KPB has received grant support from Welcome/MRC, NIHR, Parkinsons's UK and EU Horizon 2020. He receives royalties from publication of the Oxford Specialist Handbook Parkinson's Disease and Other Movement Disorders (Oxford University Press, 2008), of Marsden's Book of Movement Disorders (Oxford University Press, 2012), and of Case Studies in Movement Disorders–Common and uncommon presentations (Cambridge University Press, 2017). He has received honoraria/personal compensation for participating as consultant/scientific board member from Ipsen, Allergan, Merz and honoraria for speaking at meetings and from Allergan, Ipsen, Merz, Sun Pharma, Teva, UCB Pharmaceuticals and from the American Academy of Neurology and the International Parkinson's Disease and Movement Disorders Society. All other authors have no disclosures.

Conflict of interest related to the current work

None.

Funding related to the current work

None.

References

[1] M. Avenali, R. De Icco, M. Tinazzi, G. Defazio, L. Tronconi, G. Sandrini, et al., Pain in focal dystonias – a focused review to address an important component of the disease, Park. Relat. Disord. 54 (2018) 17–24.
[2] A.R. Harrison, J.P. Erickson, J.S. Anderson, M.S. Lee, Pain relief in patients receiving periocular botulinum toxin A, Ophthalmic Plast. Reconstr. Surg. 24 (2008) 113–116.
[3] J. Müller, J. Wissel, G. Kemmler, B. Voller, T. Bodner, A. Schneider, et al., Craniocervical dystonia questionnaire (CDQ-24): development and validation of a disease-specific quality of life instrument, J. Neurol. Neurosurg. Psychiatry 75 (2004) 749–753.
[4] O. Kutvonen, P. Dastidar, T. Nurmikko, Pain in spasmodic torticollis, Pain 69 (1997) 279–286.
[5] I.T. Lorentz, S.S. Subramaniam, C. Yiannikas, Treatment of idiopathic torticollis with botulinum Toxin A: a double-blind study on twenty-three patients, Mov. Disord. 6 (1991) 145–150.
[6] J.D. Blackie, A.J. Lees, Botulinum toxin treatment in spasmodic torticollis, J. Neurol. Neurosurg. Psychiatry 53 (1990) 640–643.
[7] J. Kulisevsky, A. Lleo, A. Gironell, J. Molet, B. Pascual-Sedano, P. Parés, Bilateral pallidal stimulation for cervical dystonia: dissociated pain and motor improvement, Neurology 55 (2000) 1754–1755.
[8] F. Cacciola, J.O. Farah, P.R. Eldridge, P. Byrne, T.K. Varma, Bilateral deep brain stimulation for cervical dystonia: long-term outcome in a series of 10 patients, Neurosurgery 67 (2010) 957–963.
[9] L. Garcia-Larrea, M. Frot, M. Valeriani, Brain generators of laser-evoked potentials: from dipoles to functional significance, Neurophysiol. Clin. 33 (2003) 279–292.
[10] M. Tinazzi, M. Valeriani, G. Squintani, F. Corrà, S. Recchia, G. Defazio, et al., Nociceptive pathway function is normal in cervical dystonia: a study using laser-evoked potentials, J. Neurol. 259 (2012) 2060–2066.
[11] S. Watanabe, R. Kakigi, M. Hoshiyama, Y. Kitamura, S. Koyama, M. Shimojo, Effects of noxious cooling of the skin on pain perception in man, J. Neurol. Sci. 135 (1996) 68–73.
[12] C.L. Comella, S. Leurgans, J. Wuu, G.T. Stebbins, T. ChmuraDystonia Study Group, Rating scales for dystonia: a multicenter assessment, Mov. Disord 18 (2003) 303–312.
[13] S. Zambito-Marsala, R. Erro, R. Bacchin, A. Fornasier, F. Fabris, C. Lo Cascio, et al., Abnormal nociceptive processing occurs centrally and not peripherally in pain-free Parkinson disease patients: a study with laser-evoked potentials, Park. Relat. Disord. 34 (2017) 43–48.
[14] G. van Wijk, D.S. Veldhuijzen, Perspective on diffuse noxious inhibitory controls as a model of endogenous pain modulation in clinical pain syndromes, J. Pain 11 (2010) 408–419.
[15] D. Le Bars, A.H. Dickenson, J.M. Besson, Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat, Pain 6 (1979) 283–304.
[16] T. De Broucker, P. Cesaro, J.C. Willer, D. Le Bars, Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract, Brain 113 (1990) 1223–1234.
[17] B.A. Vogt, Cingulate Neurobiology and Disease, Oxford University Press, 2009.
[18] E.H. Chudler, W.K. Dong, The role of the basal ganglia in nociception and pain, Pain 60 (1995) 3–38.
[19] A.J. Blood, J.K. Kuster, S.C. Woodman, N. Kirlic, M.L. Makhlouf, T.J. Multhaupt-Buell, et al., Evidence for altered basal ganglia-brainstem connections in cervical dystonia, PLoS One 7 (2012) e31654.
[20] M. Tinazzi, M. Fiorio, A. Fiaschi, J.C. Rothwell, K.P. Bhatia, Sensory functions in dystonia: insights from behavioral studies, Mov. Disord. 24 (2009) 1427–1436.