



Demographic and clinical determinants of neck pain in idiopathic cervical dystonia

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Abstract

Cervical dystonia is associated with neck pain in a significant proportion of cases, but the mechanisms underlying pain are largely unknown. In this exploratory study, we compared demographic and clinical variables in cervical dystonia patients with and without neck pain from the Italian Dystonia Registry. Univariable and multivariable logistic regression analysis indicated a higher frequency of sensory trick and a lower educational level among patients with pain.

Keywords Cervical dystonia · Pain · Basal ganglia · Nociception · Sensory trick

Introduction

Cervical dystonia (CD), is characterized by abnormal patterned head movement/posture due to involuntary contraction of the neck muscles (Castagna and Albanese 2019; Defazio et al. 2017). CD is associated with neck pain in up to 75% of cases which significantly contributes to disability and poor quality of life (Avenali et al. 2018; Charles et al. 2014).

The mechanisms underlying pain in CD are still largely unknown. Pain cannot be entirely attributed to muscle over-activity because botulinum toxin improves CD and pain to different degrees (Blackie and Lees 1990; Kulisevsky et al. 2000). Most likely, a central mechanism contributes to pain in CD, as suggested by a decrease in conditioned pain modulation (Tinazzi et al. 2019). Anomalies in descending pain inhibitory control are present in CD patients with and

without pain (Tinazzi et al. 2019), thus predisposing patients to pain, though other additional factors might be involved for the pain to manifest. Whether the demographic/clinical features of CD patients contribute to pain development has not been fully addressed to date.

In this exploratory cross-sectional study involving a large cohort of CD patients, we assessed several demographic and clinical variables for their possible association with neck pain.

Methods

Data were retrieved from the Italian Dystonia Registry (IDR) (Defazio et al. 2017). We selected patients (> 18 years) listed in the IDR as of December 2018 who had received a diagnosis of idiopathic adult-onset CD, either focal or as part of a segmental/multifocal dystonia, according to published criteria (Albanese et al. 2013). CD patients were stratified according to the presence of neck pain for 3 months or longer. The two groups were compared for age at dystonia onset and dystonia-associated

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features [e.g., tremor and sensory trick (ST)]; family history of dystonia as reported via a validated self-administered questionnaire (Aniello et al. 2006); neck/trunk trauma prior to the onset of pain and severe enough to require medical attention/hospitalization/surgery (Defazio et al. 2020); lifetime history of depression diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria on the basis of medical records reported by patients; and lifetime medical conditions associated with/predisposing patients to pain (e.g., osteoporosis, rheumatic disease, arthritis, etc.). The study was approved by the Ethics Committee of the University of Cagliari (Prot. PG/2018/11698).

Unless otherwise indicated, all values are expressed as the mean $\pm$ standard deviation (SD). Data were analyzed by the Stata statistical software (StataCorp, College Station, TX, USA). Logistic regression models with an unequal case/control ratio were used to assess the relationship between demographic/clinical variables and pain status. Odds ratios (ORs), two-sided 95% confidence intervals (95% CI), and p values (likelihood ratio statistic) were calculated. Multivariate analysis was performed according to a model-building strategy devised by Hosmer and Lemeshow (1989) using a 0.5 level at the univariate test as a screening criterion for selecting candidate variables. After fitting the model containing the selected variables, we deleted the non-significant ones and fitted a new model. The importance of variables was assessed by examining the significance of each p value and comparing the estimated ORs between the new and the old models. Bonferroni correction was adopted for multiple analyses, and the Bonferroni corrected p value was 0.01 (0.05/5 variables). To check for type II error, the statistical power relative to each variable was assessed using the Schlesselman equation for unmatched studies with an

unequal case/control ratio, assuming a two-fold increase in the risk of pain (two-sided) with $p < 0.05$.

Results

The study population was 603 patients with idiopathic adult-onset CD, either focal ($n = 417$) or as part of a segmental/multifocal dystonia ($n = 186$). Since there was no significant difference in demographic/clinical features between patients with focal and those with multifocal/segmental dystonia ($p > 0.05$; data not shown), the two groups were analyzed together. The sample was composed of 398 women and 205 men aged 61.8 ± 13.7 years; the mean years of schooling were 10.1 ± 4.4 years and the mean disease duration was 12.6 ± 10.2 years. CD was associated with tremor in 318/603 (53%) and with an effective ST in 219/603 (36.3%). Neck pain was reported by 347/603 (57%), but only 72/603 (12%) reported a medical condition associated with/predisposing to pain. There was an inverse correlation between ST and disease duration (Spearman's $\rho = -0.44$; $p = 0.03$).

On univariable analysis, CD patients with and without pain were similar for most demographic/clinical variables (Table 1). However, painful CD patients showed fewer years of schooling and a higher frequency of ST (Table 1). The study had an estimated $< 80\%$ chance of detecting a threefold modification in the risk of being associated with pain, with $\alpha = 0.05$ (two-sided) for neck/trunk trauma and depression. The other variables yielded a study power $> 90\%$.

The main effects model indicated sensory trick and lower educational level as significant independent predictors for pain (Table 2). Estimates did not change substantially when the patients with a medical condition associated with/predisposing to pain were excluded from analysis (Table 2).

Table 1 Demographic and clinical comparison of the patients included and stratified according to the presence of neck pain

	Cervical dystonia patients with pain ($n.347$)	Cervical dystonia patients without pain ($n.256$)	Odds ratio (univariable analysis)	95% confidence interval	p
Women sex (%)	233 (67.2%)	165 (64.5%)	1.06	0.75–1.48	0.74
Education (mean $\pm$ SD)	9.64 ± 4.3	10.7 ± 4.4	0.96	0.91–1.0002	0.05
Disease duration (mean $\pm$ SD)	13.3 ± 10.9	12.4 ± 10	1.006	0.99–1.02	0.49
Age at disease onset (mean $\pm$ SD)	47.9 ± 14.6	50.6 ± 14.6	1.00005	0.99–1.002	0.93
Clinical features [n . patients (%)]					
Head tremor	193 (55.6%)	125 (48.8%)	1.24	0.90–1.73	0.18
Sensory trick	155 (44.7%)	64 (25%)	2.56	1.79–3.65	< 0.001
Focal dystonia	235 (67.7%)	182 (71.1%)	0.91	0.64–1.31	0.64
Family history of dystonia	51 (14.7%)	41 (16%)	0.93	0.59–1.45	0.75
Neck/trunk trauma	10 (2.9%)	1 (0.4%)	3.09	0.087–11.1	0.08
Lifetime history of depression	15 (4.3%)	10 (3.9%)	1.14	0.5–2.6	0.75
Medical disease associated with or predisposing patients to pain	48 (13.8%)	24 (9.4%)	1.6	0.94–2.68	0.08

Table 2 Main effect models of multivariable logistic regression analysis

	Odds ratio	95% Confidence interval	<i>p</i>
Multivariable analysis in the whole sample			
Education	0.94	0.91–0.98	0.006
Sensory trick	2.15	1.49–3.11	< 0.001
Multivariable analysis after excluding patients with medical conditions associated with or predisposing to pain			
Education	0.95	0.91–0.99	0.049
Sensory trick	2.21	1.42–3.42	< 0.001

Discussion

Our analysis indicated ST and lower educational levels as independent predictors of neck pain in idiopathic adult-onset CD. In contrast, age, disease duration, head tremor, distribution and family history of dystonia, prior neck/trunk trauma, lifetime history of depression, and medical condition associated with/predisposing to pain were not associated with neck pain. Most of the negative findings were very likely valid since all the variables except neck/trunk trauma and depression reached satisfactory study power.

The association between neck pain and ST is a novel finding that may have several explanations. Aside from a chance finding, neck pain might prompt patients to develop ST, a self-developed manoeuvre that may relieve both abnormal posture and pain intensity (Ramos et al. 2014). Information on why and how patients developed their sensory trick was lacking, which precluded exploration of this hypothesis. An alternative explanation is that neck pain and sensory trick might share common pathophysiological mechanisms. A growing body of evidence has linked both ST and pain processing to specific areas of the cerebellum (Kim et al. 2017; Brugger et al. 2019). Plasticity-based remodeling of the sensorimotor areas probably plays a direct role in the pathophysiology of dystonia, i.e. in the attenuation of abnormal muscle activity during an ST, as well as in the development of chronic pain symptoms (Brugger et al. 2019; Coombes and Misra 2016; Baarbé et al. 2018; Naumann et al. 2000). Our observation of an association between neck pain and lower educational level in CD is shared by previous studies in neck/trunk pain and other painful conditions of various aetiology in diverse populations (Martinen et al. 2019; Conte et al. 2019). The mechanisms underlying such association still remain a matter of debate. Hence education may affect not only the access to the health system but also the impact and report of pain in individual patients.

We believe that our study design and procedures minimized most biases inherent to retrospective case–control study. Recruiting consecutive patients in a multicenter setting created a cohort similar to the general population of

cases (Defazio et al. 2017; Avenali et al. 2018; Albanese et al. 2013). Although the educational level was lower in the CD patients with pain and the repeatability of information was not verified, differential recall between patients with and without pain was unlikely for most variables because study populations were closely matched for degree of medical surveillance, clinical features, and disease duration. Data on lifetime history of depression were retrieved from patients' self-reports/records, which may have underestimated the condition. Bias caused by the assessors being unblinded to pain status was also unlikely since the assessors were unaware of the study hypothesis. The frequency of ST in our population was lower than in previous samples. This may have been due to the fact that ST tends to appear early in the course of the disease and lose its effectiveness with advancing disease duration. Accordingly, we found an inverse correlation between disease duration and ST (Ramos et al. 2014). Our analysis did not take into account the use of pain medications, botulinum toxin therapy, or dystonia severity. The contribution of these factors to pain may be a subject for future studies. The inclusion of patients with medical conditions associated with/predisposing to pain may have confounded neck pain classification. However, excluding these subjects from the analysis did not substantially change estimates. Owing to unsatisfactory study power, we cannot draw any definite conclusions on the possible association between pain and neck trauma or depression.

These limitations notwithstanding, our findings suggest a relationship between pain and ST. The findings are consistent with the known abnormal processing of sensory stimuli in dystonia (Conte et al. 2019), a concept that could theoretically be extended to the nociceptive system. Our findings also suggest that factors related to educational level might modulate the clinical expression and reporting of pain in CD, as has been observed for other chronic painful conditions. Information about the mechanisms underlying pain, ST, and educational level in CD is scarce and precludes definite conclusions on the associations we found. There is a need for further research in this area.

Author contributions MT and GD conceived the study, performed the analysis, and reviewed the manuscript. MT and RE wrote the first draft. All other authors contributed to data collection and reviewed the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest related to the current work.

Ethical approval This study was approved by the local Ethics Committee and was performed according to the Declaration of Helsinki. We also confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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