

Mood disorder affects age at onset of adult-onset cervical dystonia[☆]

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ABSTRACT

Introduction: Mood disorder is common in cervical dystonia, affects quality of life and may precede the onset of the dystonia. There is controversy as to whether mood disorder is part of the primary process or secondary to the disability. We assessed the characteristics of cervical dystonia patients in relation to a past history of mood disorder.

Methods: At a University Hospital clinic, in all consenting patients with cervical dystonia, we uniformly collected demographic data, medical history, and prospectively, measures of prevalent mood disorder.

Results: In 193 patients (128 women and 65 men) mean age at onset was 43.9 years and mean duration of cervical dystonia was 17.5 years. Men had earlier age at onset of cervical dystonia than women ($p = 0.0037$). A history of a mood disorder was reported in 53/128 (41%) women with a significantly earlier median age at onset of cervical dystonia (42 years) than 75/128 (59%) women with no history of mood disorder (48 years) ($p = 0.005$); 33 (26%) women with mood disorder prior to dystonia also had an earlier age at onset of dystonia than the 75 without such a history ($p = 0.0154$). A history of mood disorder was more common in women (41%) than men (31%); 54/128 (42%) women and 21/65 (32%) men had current mood disorder symptoms.

Conclusions: In our cervical dystonia clinic population significant differences in the age at onset in women with, and without, a history of mood disorder strongly indicates that anxiety and depression are primary non-motor (and premotor) symptoms of cervical dystonia.

1. Introduction

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements and postures [1]. Focal isolated dystonia, affecting muscles in a particular anatomical distribution, with or without tremor, and no other neurological signs, is the most common type of adult-onset dystonia. Cervical dystonia is the most prevalent form of adult onset dystonia worldwide; both its aetiology and pathogenesis are poorly understood. Psychiatric symptoms, especially anxiety and depression, are commonly observed occurring in 30–60% of cervical dystonia patients [2–13].

There is debate as to whether the mood disorder is secondary to the stigma of a socially obvious movement disorder or is a primary symptom, caused by the same disordered neurobiological processes driving the abnormal movements. In support of the latter concept, it has been observed that depression and/or anxiety may precede the onset of the dystonic motor symptoms, often by many years [13]. In this study, we assessed the history of, and

prevalence of, mood disorder of patients attending a single-center, tertiary hospital with cervical dystonia in relation to their demographic variables.

2. Methods

2.1. Study participants

The study participants were recruited from a database of dystonia patients attending the botulinum toxin clinic at a single tertiary hospital, where >60% of the clinically diagnosed cervical dystonia patients in the Republic of Ireland are treated [14] from July 2018 to April 2019. We conducted a cross-sectional study of all consenting patients with adult-onset cervical dystonia, diagnosed by two experienced movement disorders neurologists according to the standard diagnostic criteria [1]. We excluded patients with other forms of dystonia including, generalized dystonia, segmental disorder and other focal dystonias, other neurological disorders and other comorbidities (cognitive impairment) which precluded completion of questionnaires utilized in this study.

2.2. Assessment instruments

Using a questionnaire designed specifically for our study, we collected basic demographic information from our patients including age at the time of study, age at onset of cervical dystonia, duration of cervical

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dystonia, history of a medical diagnosis of anxiety or depression (given by any medical practitioner), time of onset of anxiety or depression relative to onset of cervical dystonia and other medical background history. We used the revised Toronto Western Spasmodic Torticollis Ratings Scale – 2 Pain (TWSTRS-2 Pain) and the pain subscale of the Cervical Dystonia Impact Profile – 58 (CDIP-58) to assess pain. These questionnaires are all validated rating scales with high reliability for use in both clinical and non-clinical settings [15]. We used the Beck Anxiety Inventory (BAI) and Beck Depression Inventory, second edition (BDI-II) to assess current anxiety and/or depression symptoms. The BAI and BDI-II are both 21-item self-report assessment tools for anxiety and depression respectively. They are each rated on a 4-point scale from 0 to 3 with a maximum total score of 63 each [16–21]. The patients were recruited on the day of their scheduled appointment for botulinum toxin injection. For the TWSTRS-2 Pain scale, CDIP-58, BAI and BDI, the patients were required to fill these questionnaires within one week of receiving their botulinum toxin injection and the questionnaires referred to symptoms in the last 2 weeks at the time of filling out the questionnaire. This reflects the period at which the botulinum toxin effect has worn off or is minimal. When a questionnaire was incorrectly/incompletely filled out, the patient was contacted again at their next 3-monthly appointment for botulinum toxin injection. The majority of the patients filled out all their questionnaires on the day they were recruited, others took them home and posted them back within the one week advised. As the study period was from July 2018 to April 2019 with patients attending for botulinum toxin injection 3-monthly, patients who failed to correctly/completely fill out their questionnaires after 4 attempts at recruitment were not included.

2.3. Statistical analysis

We tested our variables for normality and lognormality using Anderson-Darling, D'Agostino & Pearson, Shapiro-Wilk, and Kolmogorov-Smirnov tests. The Anderson-Darling and Komogorov-Smirnov tests showed a normal distribution for only the age at time of study and age at onset variable. Given the non-Gaussian distribution of our data we used non-parametric tests for analysis. Means with standard deviation, medians and interquartile range (IQR) were used to describe the distribution of our data set. We used the Mann-Whitney (M-W) test to compare the differences between two independent groups with dependent variables. Significance level was defined as $p < 0.05$.

2.4. Study protocols

The study was reviewed and approved by the St Vincent's Healthcare Group Ethics and Medical Research Committee. All participants gave written informed consent prior to their participation in the study.

3. Results

3.1. Study cohort characteristics

213 cervical dystonia patients fulfilled our study criteria; two patients did not consent to participate in the study and 18, who did not fully complete the questionnaires, were excluded, leaving 193 for analysis (Table 1). The 193 patients {128 (66%) women and 65 (34%) men} had a mean age (\pm Standard Deviation) of 61.7 (\pm 13.0) years; mean age at onset of cervical dystonia was 43.9 (\pm 12.9) years, mean duration of cervical dystonia was 17.5 (\pm 11.7) years, mean TWSTRS-2 Pain was 13.57 (\pm 9.8) and mean Pain subscale of CDIP-58 was 45.22 (\pm 30.47) (Table 1).

3.2. Sex and age at onset of cervical dystonia

The 65 men had a significantly earlier age of onset of cervical dystonia than the 128 women (Fig. 1) {Men's age at onset: mean 40.0 \pm 12.0 years; median 41.0 years (IQR 28.5–50). Women's age at onset: mean 45.9 \pm

12.7 years; median 46 years (IQR 36.5–55.8); $p = 0.0037$ (M-W U = 3100) (Table 1)}.

3.3. History of anxiety or depression and age at onset of cervical dystonia

Although commoner in women, there was no significant sex difference in the frequencies of a history of anxiety or depression, both before and after the onset of motor symptoms of cervical dystonia. Of the 128 women, 53 (41%) reported a medical history of anxiety and/or depression; 33 (26%) had onset of mood disorder *prior to* the development of cervical dystonia (median duration prior: 10.0 years; IQR: 5–17 years). Of the 65 men, 21 (32%) reported a history of anxiety and/or depression with 11 (17%) prior to the onset of cervical dystonia (median duration prior: 2.0 years; IQR: 2–15 years).

The 53 women with a history of anxiety and/or depression at any time had significantly earlier age at onset of cervical dystonia (Mean: 42.3 \pm 11.7 years; Median 42 years, IQR = 32–50) than the 75 women with no history of mood disorder {Mean: 48.5 \pm 12.8 years; Median: 48 years, IQR = 41–58; ($p = 0.005$; M-W U = 1412)} (Table 1 & Fig. 2).

In 21 men with history of anxiety and/or depression, the age at onset of cervical dystonia was non-significantly earlier {Mean: 38.8 \pm 13.1 years; Median: 39 years (IQR = 26.5–51)} than the age at onset in 44 men without a history of anxiety and/or depression {Mean: 40.4 \pm 12.0 years; Median: 42 years (IQR = 30–50.8) ($p = 0.613$; M-W U = 425.5)}.

3.4. History of anxiety or depression prior to onset of cervical dystonia and age at onset

We further compared the age at onset between 33 women with a history of anxiety and/or depression preceding the onset of cervical dystonia and 75 women without any history of anxiety and/or depression; 33 women with mood disorder preceding the onset of cervical dystonia had a significantly earlier onset of dystonia than the 75 women with no history of mood disorder {Mean: 42.5 \pm 10.7; Median: 42 (IQR 32.5–50.0) and Mean 48.5 \pm 12.8; Median: 48.0 (IQR 41.0–58.0) respectively. $p = 0.0154$ (M-W U 876)}.

3.5. No history of anxiety or depression and age at onset of cervical dystonia

There were 44/65 (68%) men and 75/128 (59%) women with no medical history of depression or anxiety. The 44 men had a significantly earlier age at onset of cervical dystonia than the 75 women {Men's age at onset: mean 40.4 \pm 12.0 years; median 42 years (IQR 30–50.8). Women's age at onset: mean 48.5 \pm 12.8 years; median 48 years (IQR 41–58), $p = 0.0014$ (M-W U = 1075)}.

3.6. Current anxiety/depression symptoms & age at onset of cervical dystonia

Using the BAI and BDI-II, with scores >13 for each assessment tool representing evidence of anxiety or depression symptoms, 54/128 (42%) women and 21/65 (32%) men reported current anxiety and/or depression symptoms. The age at onset of 54 women with **current** anxiety and/or depression symptoms (mean = 44.1 \pm 11.8 years; median: 43 years; IQR 33–52.3) was non-significantly earlier than the 74 women without current anxiety and/or depression (Mean: 47.3 \pm 13.2 years; median: 48 years, IQR 40–56.3) ($p = 0.1062$; M-W U = 1663). Similarly, the age at onset of 21 men with current mood disorder was non-significantly earlier than the 44 men without current anxiety/depression {Mean: 38.8 \pm 13.1 years; median: 39 years, IQR 26.5–51, and mean: 40.0 \pm 12.0 years; median: 42 years, IQR 30–50 respectively ($p = 0.694$, M-W U = 423.5)}.

Of the 74/128 (58%) women and 44/65 (68%) men who scored ≤ 13 on the BAI and BDI, indicating no current anxiety or depressive symptoms; 19/74 (26%) women and 8/44 (18%) men reported a history of medically diagnosed anxiety and/or depression.

Table 1
Sex, history of mood disorder, pain and age at onset of cervical dystonia.

Cervical dystonia patient group (N)	Age at onset (y) Mean ± SD Median (IQR)	Statistical comparison Mann-Whitney test (MW-U)	Duration of cervical dystonia (y) Mean ± SD Median (IQR)	Statistical comparison Mann-Whitney test (MW-U)	TWSTRS Pain Mean ± SD Median (IQR)	Statistical comparison Mann-Whitney test (MW-U)	CDIP-58 (Pain subscale) Mean ± SD Median (IQR)	Statistical comparison Mann-Whitney test (MW-U)
Total group (193)	43.9 ± 12.9 45.0 (33.3–52.8)	na		na	13.57 ± 9.822 14 (0–42)	na	45.22 ± 30.47 45 (0–100)	na
All women (128)	45.9 ± 12.7 46 (36.5–55.8)	p = 0.0037 MW-U = 3100	16.8 ± 11.7 14.5 (8.0–22.8)	p = 0.206 MW-U = 3696	14.64 ± 10.2 14 (0–42)	p = 0.0794 MW-U = 3373	48.69 ± 27.7 58 (0–100)	p = 0.0431 MW-U = 3278
All men (65)	40.0 ± 12.0 41.0 (28.5–50)		18.5 ± 11.4 18.0 (7.3–28)		11.74 ± 8.18 13 (0–37)		39.69 ± 27.69 37.5 (0–100)	
Women with h/o depression/anxiety (53)	42.3 ± 11.7 42 (32–50)	p = 0.005 MW-U = 1412	16.9 ± 13.2 13 (6.5–23)	p = 0.617 MW-U = 1884	16.61 ± 10.48 16.5 (0–42)	p = 0.0719 MW-U = 1649	53.57 ± 29.39 57.5 (0–100)	p = 0.1215 MW-U = 1701
Women with NO h/o depression/anxiety (75)	48.5 ± 12.8 48 (41–58)		17.0 ± 10.5 15.0 (9–22)		13.13 ± 9.801 13 (0–33)		44.53 ± 27.3 40 (0–100)	
Men with h/o depression/anxiety (21)	38.8 ± 13.1 39 (26.5–51)	p = 0.613 MW-U = 425.5	21.7 ± 12.8 21 (11.5–29)	p = 0.204 MW-U = 371	10.85 ± 8.177 10 (0–33)	p = 0.6342 MW-U = 388	43.25 ± 27.3 19 (0–100)	p = 0.3128 MW-U = 352.5
Men with NO h/o depression/anxiety (44)	40.4 ± 12.0 42 (30–50.8)		16.9 ± 10.5 16 (7–25)		12.43 ± 9.213 14 (0–37)		36.19 ± 26.41 32.5 (0–100)	

Age at onset of cervical dystonia and duration of illness in years (y) in 193 cervical dystonia patients, with mean (±SD) and median {with interquartile ranges (IQR)} with Mann-Whitney (M-W) comparisons and level of significance. There were 128/193 (66%) women and 65/193 (34%) men; both women and men were subdivided according to a reported history of mood disorder. All men had a significantly earlier age at onset of cervical dystonia than all women. Women with a history of mood disorder had a significantly earlier onset than women with no such history. No significant difference was found in the ages at onset of men with, and without, a history of mood disorder. All women had a significantly worse CDIP-58 Pain subscale scores than all women.

3.6.1. Pain and history of anxiety and/or depression

There was a significant difference between 128 women and 65 men in their CDIP-58 Pain subscale scores with women having worse pain scores

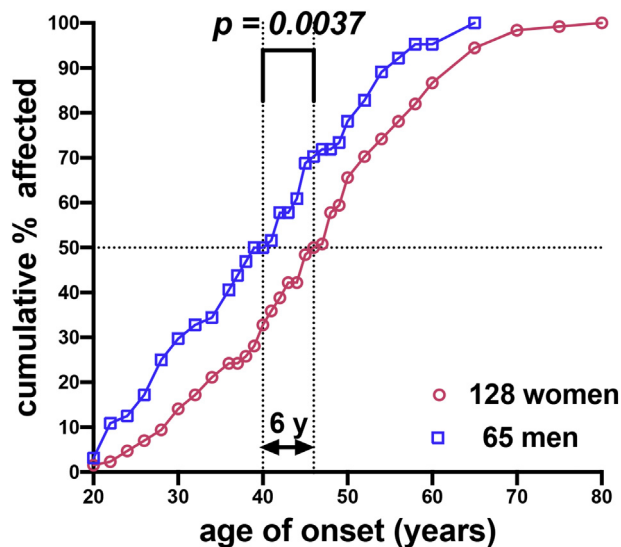


Fig. 1. Cumulative percentage affected by age at onset of cervical dystonia for 65/193 men (blue squares and connecting lines) and 128/193 women (red circles and connecting line). The 65 men had median age at onset of CD of 41 years; the 128 women had median age at onset of CD of 46 years (P = 0.0037; Mann-Whitney; see Table 1).

{Mean: 48.69 ± 27.7; Median: 58 (IQR 0–100) and Mean 39.69 ± 27.69; Median: 37.5 (IQR 0–100) respectively. p = 0.0431 (M-W U 3278)} but there was no significant difference between 128 women and 65 men in their TWSTRS-2 Pain scores {Women - Mean: 14.64 ± 10.2; Median: 14 (IQR 0–42) and Men - Mean 11.74 ± 8.18; Median: 13 (IQR 0–37) respectively. p = 0.0794 (M-W U 3373)}. There was no significant difference in CDIP-58 Pain subscale scores and TWSTRS-2 Pain score when the 53 women with a history of anxiety and/or depression were compared to the 75 women without a history of anxiety and/or depression. This was also similar when 21 men with a history of anxiety and/or depression were compared to 44 men without a history of anxiety and/or depression (Table 1).

3.6.2. Other comorbidities and marital status

There were no significant differences in the prevalence of comorbidities between CD patients with and without a history of mood disorder (Table 2). The most prevalent medical diagnosis was hypertension; this was similar across all 3 subgroups (16% in all participants, 20% in the participants with a history of mood disorder at any time, 12.6% in the group without mood disorder and 16% in the group with a history of mood disorder preceding the onset of CD. Other comorbidities included hypercholesterolemia, hypothyroidism, asthma/chronic obstructive pulmonary disease (COPD), gastro-oesophageal reflux disease, atrial fibrillation, arthritis, diabetes mellitus II, epilepsy, overactive bladder, myocardial infarction, peripheral vascular disease and breast cancer in remission. Amongst the participants with mood disorder, none had asthma/COPD, atrial fibrillation, over active bladder, myocardial infarction or breast cancer.

Marital status was similar across all groups except in the group with a history of mood disorder who reported 12% separated; this was twice more common than the group without a history of mood disorder, although still relatively low (Table 2).

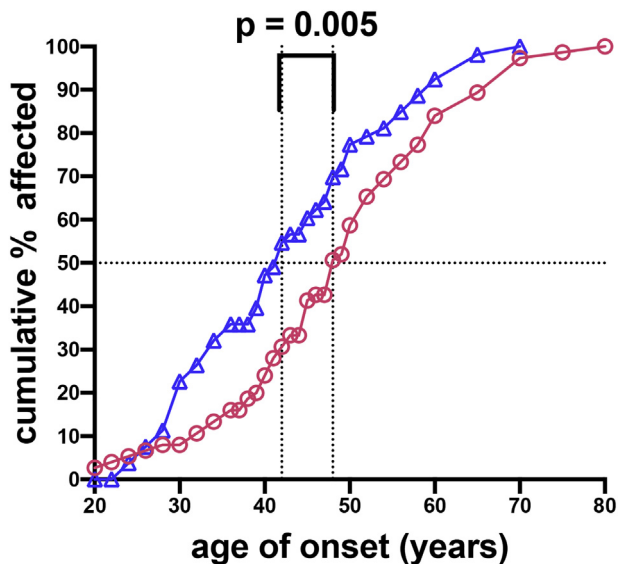


Fig. 2. Cumulative percentage affected by age at onset of cervical dystonia for 53/128 women with a history of mood disorder (blue triangles and connecting line) and 75/128 women with no history of a mood disorder (red circles and connecting line). The 53 women with mood disorder history had a median age at onset of CD of 42 years; the 75 women with no such history had a median age at onset of CD of 48 years ($p = 0.005$; Mann-Whitney; see Table 1).

4. Discussion

In this comprehensive, single-center survey of patients with adult-onset cervical dystonia we found that men had significantly earlier age at onset of cervical dystonia than women; this has been previously reported [22,23]. Men not reporting a medical history of depression or anxiety also had a significantly earlier age at onset than women without a history of mood disorder.

The most important, novel, observation in this study is that women reporting a history of anxiety and/or depression, at any stage, had a significantly earlier age at onset of cervical dystonia than women not reporting anxiety and/or depression. We also found that women with a history of anxiety and/or depression preceding the onset of motor symptoms had a significantly earlier age at onset of cervical dystonia, when compared to women without any history of mood disorder.

In the case of men, while those reporting a history of anxiety and/or depression also had earlier age at onset of cervical dystonia, when compared to men without such a history, this difference was not statistically significant. The latter, non-significant finding, may be a Type-2 error, given the relatively smaller numbers of male cervical dystonia patients in our study cohort.

One possible explanation of the effect of preceding mood disorder and earlier age at onset of motor symptoms might be that patients, reporting a history mood disorder, are more likely to be under medical surveillance and thus their dystonia might be more quickly diagnosed. We consider this is an unlikely explanation, given the six-year difference in reported median ages of onset in the two groups of women (with and without mood disorder).

Our findings also confirm the accumulating evidence of the co-existence of anxiety and depression with cervical dystonia [2–13]. In our study, 41% of women and 32% of men (38.3% of all 193 participants) reported a past history of anxiety and/or depression, which preceded motor symptoms in 26% women & 17% of men. Current anxiety and/or depression symptoms (by the BAI and BDI-II) were, non-significantly, more common in women (43% women and 36% men). Patients with current anxiety and/or depression symptoms, as shown by the BAI & BDI-II, had an earlier age at onset of

cervical dystonia when compared with those without, but this was not statistically significant. A possible explanation for this is that, while BAI & BDI-II are reliable and validated assessment tools for assessing anxiety and depression [16–21], they were designed as screening rather than diagnostic tools, reporting the extent to which patient has anxiety and depressive symptoms in “the week preceding” their completion of the questionnaires [24–26]. Another limitation of BAI & BDI is that, in participants with concomitant physical illness, their reliance on symptoms such as fatigue, tingling, etc., may artificially influence scores due to symptoms related to the physical disorder, rather than due to mood disorder. In addition, of the 118 patients who scored ≤ 13 indicating no current anxiety and/or depression symptoms, 27 patients (19 women and 8 men) had an established history of medically diagnosed anxiety and/or depression. The normal scores in these patients could probably be explained by an improvement of anxiety and/or depressive symptoms due to the effectiveness of ongoing treatment of the mood disorders. This is one of the intended uses of BAI & BDI-II [24–26].

Pain was more prevalent in the group with a history of anxiety and/or depression when compared to the group without. A possible explanation for this could be that pain predisposed this group to anxiety and/or depression; another explanation is that CD patients with a clinical history of anxiety and/or depression may report more distress in relation to pain.

The strength of this study is that it comes from a large single University Hospital with some patients attending for as long as 30 years. Given that botulinum toxin is the most effective therapy for CD, this seemed to be the most appropriate form of recruitment of this group of patients; we estimate that we treat 60% of the cervical dystonia patient population in Ireland and the overwhelming majority of patients had been seen within two years after onset of CD symptoms. The limitations in the study include a necessarily retrospective patient-report of the time of onset of mood disorder in relation to the onset of their cervical dystonia (but recorded in

Table 2 Demographic (Comorbidities in order of prevalence and marital status).

	All participants (193) n (%)	Participants with a history of mood disorder at anytime (74) n (%)	Participants without a history of mood disorder (119) n (%)	Participants with a history of mood disorder preceding CD onset (44) n (%)
Other comorbidities excluding mood disorder				
None	128 (66%)	45 (60.8%)	83 (69.7%)	28 (63.6%)
Hypertension	30 (15.5%)	15 (20.3%)	15 (12.6%)	7 (15.9%)
Hypercholesterolemia	22 (11.4%)	12 (16.2%)	10 (8.4%)	6 (13.6%)
Hypothyroidism	14 (7.3%)	6 (8.1%)	8 (6.7%)	1 (2.3%)
Asthma/COPD	5 (2.6%)	0	5 (4.2%)	0
Gastro-oesophageal reflux disease	4 (2.1%)	1 (1.4%)	3 (2.5%)	1 (2.3%)
Atrial fibrillation	4 (2.1%)	0	4 (3.4%)	0
Gout/Arthritis	4 (2.1%)	2 (2.7%)	2 (1.7%)	0
Diabetes Mellitus II	2 (1%)	1 (1.4%)	1 (0.8%)	1 (2.3%)
Epilepsy	1 (0.52%)	1 (1.4%)	0	0
Overactive bladder	1 (0.52%)	0	1 (0.8%)	0
Myocardial Infarction	1 (0.53%)	0	1 (0.8%)	0
Peripheral vascular disease	1 (0.52%)	1 (1.4%)	0	0
Breast cancer in remission	1 (0.52%)	0	1 (0.8%)	0
Marital status				
Married	110 (57%)	38 (51.4%)	72 (60.5%)	21 (47.7%)
Single	43 (22.3%)	17 (23%)	26 (21.8%)	9 (20.5%)
Widow(er)	19 (9.84%)	6 (8%)	13 (10.9%)	4 (9.1%)
Separated	13 (6.74%)	9 (12.2%)	4 (3.4%)	7 (15.9%)
Divorced	8 (4.12%)	4 (5.4%)	4 (3.4%)	3 (6.8%)

Comorbidities and marital status presented as number of patients and percentage for the entire study cohort and also in groups including, group with history of mood disorder at anytime, the group without a history of mood disorder, the groups with a history of mood disorder preceding the onset of CD and the participants altogether. The comorbidities and marital status were similar across all groups.

medical notes at the time of initial presentation) and the use of BAI & BDI as measures of current mood disorder which do not distinguish between endogenous and exogenous depression.

These findings indicate that both sex and mood disorder have independent effects on age at onset of adult-onset cervical dystonia and support the concept that mood disorder is a primary non-motor and premotor symptom of cervical dystonia, reflecting disordered neurobiological mechanisms, presumably affecting the limbic system [27]. Postulated pathophysiological models of adult-onset isolated dystonia must consider these independent factors, mood disorder and sex, in relation to age at onset, in any hypothetical disordered network.

In conclusion, we have observed significant differences in the age at onset in women with and without a history of mood disorder. We consider this observation strongly indicates that anxiety and depression are primary non-motor and premotor symptoms of cervical dystonia.

Authors' roles

1. Research project: A. Conception, B. Organization, C. Execution
 - a. Ihedinachi I Ndukwe (B, C)
 - b. Sean O'Riordan (C)
 - c. Michael Hutchinson (A, B)
2. Statistical analysis: A. Design, B. Execution, C. Review and Critique
 - a. Ihedinachi Ndukwe (A, B)
 - b. Cathal B Walsh (C)
 - c. Michael Hutchinson (A, B)
3. Manuscript: A. Writing of the first draft, B. Review and Critique
 - a. Ihedinachi I Ndukwe (A, B)
 - b. Sean O'Riordan (B)
 - c. Cathal B Walsh (B)
 - d. Michael Hutchinson (A, B)

Ethics compliance statement

This study was approved by St Vincent's Healthcare Group, Ethics and Medical Research Committee (no reference number assigned). Written informed consent was obtained from all participants of the study. We 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.

Full financial disclosure for the previous 12 months

Sean O'Riordan has been employed by St. Vincent's University Hospital, Dublin; has received grant support from AbbVie, Ireland (travel grant for conference).

Michael Hutchinson: is in receipt of research grants from Dystonia Ireland, the Health Research Board of Ireland (CSA-2012-5), Dystonia Ireland, Foundation for Dystonia Research and the Irish Institute of Clinical Neuroscience.

Ihedinachi Ndukwe & Cathal B Walsh have no disclosures.

CRedit authorship contribution statement

Ihedinachi Ndukwe: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Sean O'Riordan:** Conceptualization, Investigation, Data curation, Writing - original draft, Visualization. **Michael Hutchinson:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

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