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Psychiatric Symptoms in Women with Focal Cervical Dystonia - Exploring New Pathophysiological Pathways

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Abstract - So far there is not much research considering female sex as a risk factor for developing focal cervical dystonia and concomitant psychiatric symptoms such as anxiety. New research proposes ideas of CD baseline pathophysiology targeting neurobiological mechanisms of gamma aminobutyric acid GABAergic function underlying sexual dimorphism and psychiatric symptoms as an intrinsic factor of the disease itself. Our research examines the connection between motor and non-motor symptoms in female patients suffering from focal cervical dystonia and their response to treatment, citing the available literature and hypothesizing whether it can be linked to previously described alterations in GABA levels.

Key words: anxiety; dystonic disorders; gamma-aminobutyric acid; pain

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Introduction

Cervical dystonia (CD) is the most frequent type of focal adult-onset dystonia characterized by various abnormal postures of the head [1,2,3]. According to the latest COL CAP concept concerning the distinct differentiation between dystonic muscles affecting the position of the cervical spine, there are 11 subtypes of CD that can be identified- torticollis, torticaput, laterocollis, laterocaput, retrocollis, retrocaput, anterocollis, anterocaput, lateral shift, posterior sagittal shift (combination of retrocollis and anterocaput ("double chin"), and forward sagittal shift [4]. The etiopathogenesis of the disorder is unclear, but the structures of the prefrontal cortex, brainstem, basal ganglia and cerebellum are known to be involved in the pathological process [5-10]. Currently, botulinum toxin type A (BTX - A) is considered the first line therapy for this condition [11]. Isolated cervical dystonia shows clear sex differences in both the prevalence and age of onset of the disease, appearing 3-times more often in women but presenting more early in men [12,13].

Besides motor symptoms, approximately thirty-six percent of patients with focal CD

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experience non-motor symptoms (NMs) such as pain, psychiatric disorders, cognitive impairment, sleep disorders, sensory and autonomic abnormalities [14-17]. The relationship between motor symptoms and NMs symptoms is still unclear but some research have shown no correlation of NMs severity comparing to motor symptoms suggesting the NMs as independent burden of the illness [15,17].

A recent paper of Raffee and associates presents the evidence of sex being single and the most important biological variable in relation to disease penetrance and expression in adult-onset idiopathic isolated focal dystonia [18]. CD is more prevalent in women, but men's mean age of onset is 4 years earlier than women, while women with a history of anxiety/depression, at any time, had an earlier onset of motor symptoms when compared with women with no mood disorder [19].

Recent articles propose new ideas of CD baseline pathophysiology targeting neurobiological mechanisms of gamma aminobutyric acid GABAergic function underlying the existing sexual dimorphism [20]. GABA is the main inhibitory neurotransmitter in the brain, counterbalancing the action of the excitatory neurotransmitter glutamate. Intracortical GABAergic inhibition induces the dystonic movement, while alterations in the GABA system have been linked to the pathophysiology of anxiety disorders where patients with anxiety showed lover GABA levels in comparison to healthy control group [21-24]. Women under the age of 40 have been shown to have higher levels of GABA than men but a greater age-related decline in GABA levels. Before age of 40 women show higher GABA/creatine integral ratios and faster temporal discrimination than men, which might explain earlier experiencing of motor symptoms in men compared to younger women. Later in life, GABA levels are lower in women than men, which can also explain the higher prevalence of female patients [25,26].

This study first aimed to evaluate difference between motor symptoms and NMs (pain, depression and anxiety) in CD considering sex and second to compare the effect of local botulinum-toxin therapy in both men and women.

Subjects and Methods

Study Setting and Participants

A cohort of 39 patients (12 men, 27 women) was gathered from department of Neurology, University Hospital Osijek (Croatia). All patients included in the study had a confirmed diagnosis of CD as per collum-caput (COL CAP) concept and provided a written informed consent to take part in our study [4]. The study was approved by the ethics committee of University Hospital Center Osijek. Collected data included demographic characteristics, the disease duration, patients' working status and education level, medical history, the socio-economic levels. In order to clarify whether the botulinum-toxin therapy could influence the motor symptoms and NMs, we studied the correlation between them at baseline and three weeks after the botulinum-toxin injection. Regarding the cognitive profile of our patients, all patients had undergone neurodiagnostic workup (brain MRI) for evaluating possible neurodegeneration and cerebral lesion (an exclusion criteria) and Addenbrooke's Cognitive Examination-Revised test profiling to rule out the ones with eventual mild cognitive impairment (MCI) [27]. It is a brief battery that provides evaluation of six cognitive domains totaling 100 points: orientation (10 points), attention (8 points), memory (35 points), verbal fluency (14 points), language (28 points) and visuospatial abilities (5 points). The maximum possible score is 100 with a cut-off score of 88/100 in the setting of a university hospital clinic. Individuals with score less than 83 were excluded to avoid interferences of cognitive impairment.

Clinical evaluation of motor symptoms

Motor symptoms of CD were evaluated according to adjusted TSUI scale: an impairment scale which evaluates the amplitude and duration of sustained posture and intermittent movements of the head, as well as the presence of shoulder elevation and tremor. Rotation, tilt, and sagittal movements are rated on a 0 – 3 scale for a maximum of 9. Additionally, head tremor is rated from 0 to 2 and shoulder elevation from 0 to 3. Multiplication by a duration score is performed for amplitude of sustained movements (1 = intermittent, 2 = constant) and for tremor (1 = occasional, 2 = con-

tinuous) resulting in a total possible score of 25 [28]. Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was used to determine disability due to dystonia [29]. The standard TWSTRS consists of three domains that assess motor severity, pain, and disability. The motor severity subscale consists of 10 items, with variable scaling and weighting. It also includes a disability scale with 6 items, and a pain scale with 3 items. The total score is the sum of each of the subscales.

Clinical evaluation of non-motor symptoms

Of the non-motor symptoms we evaluated pain and anxiety. To evaluate the presence and severity of anxiety we used Beck Anxiety Inventory (BAI) mood questionnaire [30]. The cut-off scores we used for BAI were: 0 – 7 minimal anxiety, 8 – 15 mild anxiety, 16 – 25 moderate anxiety, and 26 – 63 severe anxiety. According to the manual, the suggested cut-off for clinically significant anxiety on the BAI is 16. Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was used to determine severity and duration of pain as well as disability due to pain in CD.

Statistical analysis

Demographic and clinical variables were analyzed using parametric and nonparametric tests as appropriate using SPSS 23.0 software. Quantitative data was tested for normality of distribution using Shapiro-Wilks test. Parametric numerical variables were expressed as mean ± standard deviation, while non-parametric data was expressed as median and interquartile range. Categorical variables were expressed as numbers and percentages. Categorical variables were expressed as numbers and percentages and were compared using Chi-square test, or in case of small samples, Fisher's Exact Test was used. Comparison between numerical and categorical (with two groups) variables was conducted using Student's T-test (for parametric variables) or Mann-Whitney Test (for non-parametric variables). Correlation between repeated nonparametric variables was conducted using Wilcoxon Signed Rank Test. The level of significance was set on alpha = 0.05.

Results

Demographic data

We enrolled into this study a total of 39 patients who fulfilled the inclusion criteria of CD. The demographic features are reported in Table 1.

Table 1. Demographic characteristics of Croatian CD patients

Variables	CD patients (n = 39)
Age (years)	56.9 ± 11.626[a]
Level of education %	
Low	23.1 % (9)
Middle	84.6 % (24)
High	15.4 % (6)
Age at onset (years)	49.9 ± 11.197[a]
Sex (female) in %	69.2 % (27)
aMean ± SD	

The overall mean age of this study population was 56.9 ± 11.626 years. The mean age at onset of the disease was 49.9 ± 11.197 years and included 27 (69.2 %) females and 12 (30.8 %) males. Majority (24; 84.6 %) of our patients had a middle level of education. In our study, both sexes had similar demographic characteristics, including mean age, age at dystonia onset, disease duration and education.

Effect of botulinum toxin treatment

When comparing the effect of botulinum toxin treatment, positive results can be seen in pain, disability and motor symptoms, with reduction of median scores after treatment. Regarding non-motor symptoms, botulinum toxin treatment has a positive effect on orientation, attention, memory, fluency and language, while there are no significant changes in orientation, attention and fluency sub scores. These results can be seen in Table 2.

Motor aspects before and after botulinum toxin treatment regarding sex

We compared the sum of motor symptoms between men and women according to adjusted TSUI scale, with no significant difference between the two groups before and after botulinum-toxin (BTX) treatment (p = 0.183; Student's T-test). There was also no difference

Table 2. Comparison of different scores before and after botulinum toxin treatment (*SD - standard deviation, #IQR – interquartile range)

Variable	Before treatment/ median (IQR#)	After treatment/ median (IQR#)	Z	p	Stastical test
TSUI score	7 (5 - 9)	5 (3 – 6.25)	- 3.009	0.003	
TWSTR disability	13.579 (± 7.325*)	6 (2 - 13)	- 4.462	< 0.001	
TWSTR pain	7.25 (3.68 – 10.31)	4.75 (0 - 8)	- 3.212	0.001	
BAI	5.5 (1 – 19.25)	4 (2 - 15)	- 2,066	0.039	
ACE	89 80 → - 97)	95 87 → - 98)	- 3.604	< 0.001	
Orientation	10 (10 - 10)	10 (10 - 10)	0.00	1.000	Wilcoxon Signed Ranks
Attention	8 (7 - 8)	8 (6 -8)	- 0.155	0.877	
Memory	24 (17 - 25)	24 (23 - 26)	- 2.930	0.003	
Fluency	10 (7 - 12)	12 (10 - 14)	- 3.048	0.002	
Language	26 (23 - 26)	26 (25 - 26)	- 2.349	0.019	
Visuospacial function	16 (16 - 16)	16 (15 - 16)	- 1.039	0.299	

TSUI = brief rating scale for CD developed by Tsui and associates (1985, 1986,1987) and Stell and associates 1988); TWSTR = Toronto Western Spasmodic Torticollis Rating Scale; BAI = Beck Anxiety Inventory; ACE = Adenbrooke's cognitive examination test

in efficacy of BTX treatment between sexes on disability (p = 0.899; Mann-Whitney Test) and pain (p = 0.271; Mann-Whitney Test) using TWISTRS scale.

Non-motor aspects before and after botulinum toxin treatment regarding sex

In non-motor variables, there was no significant difference between the two groups concerning pain and cognitive changes before as well after BTX treatment as can be seen in Table 3. The only difference observed within the two groups was initially higher BAI in women compared to men (p = 0.004; Student's T-test) that was significantly reduced (mean difference 4) in females compared to men (mean difference - 1.5) after the BTX treatment (p = 0.033; Student's T-test). When enrolled in the study, only two of 27 women involved were previously diagnosed with anxiety disorder. Initial BAI questionnaire suggested anxious disorder in 14 female subjects (51.8 %) where seven of them expressed severe anxiety (BAI 26 - 63), while three had moderate (BAI 16 - 25) and four mild (BAI 8 - 15) anxiety symptoms according to questionnaire. After the therapy consisting in local botulinum toxin treatment,

Table 3. Comparison of mean differences of non-motor scores before and after botulinum toxin treatment regarding sex

Variable	t/Z	P	Statistical test
BAI	- 2.237	0.033	Student's T-test
Orientation	- 1.488	0.137	
Attention	- 0. 955	0.320	
Memory	- 1.225	0.221	
Fluency	- 0.586	0.560	
Language	- 1.146	0.252	
Visuospacial	- 0.158	0.874	
ACE	- 0.351	0.351	

BAI= Beck Anxiety Inventory; ACE= Adenbrooke's cognitive examination test

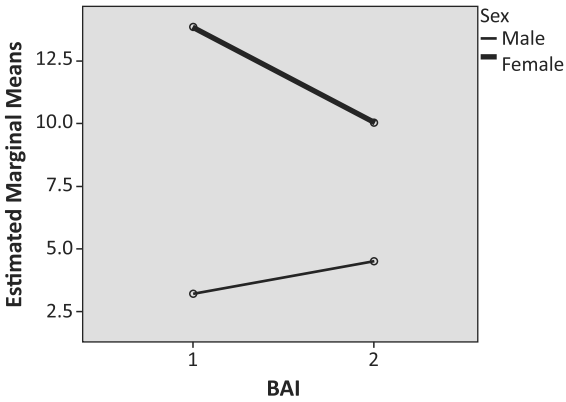

Figure 1. Sex difference regarding BAI scores before (1) and after (2) botulinum toxin treatment

anxious disorder was reported in 29 % of the patients (one severe, three moderate and three mild anxious disorder according to repeated BAI questionnaire).

The results in our research were consistent with previous findings showing the predominance of female sex with 27 (69.2 %) females and 12 (30.8 %) male subjects suffering from cervical dystonia. On the contrary to previous reports in literature suggesting 4 - 7 years earlier presentation of cervical dystonia in male sex, our results showed no statistically significant difference in illness occurrence between sexes considering the time onset of CD (mean difference 5.6 ± 11.626 p = 0.772, Mann-Whitney Test). There was also no difference in the duration of the symptoms between the male and female group (6.0 vs 5.0 years; p = 0.782, Mann-Whitney Test). Comparing the severity of motor symptoms and non-motor symptoms (pain and anxiety) between the two groups our research showed significant reduction of all symptoms after the treatment without statistically significant difference between sexes. The only notable difference between sexes was initially high BAI in female subjects compared to men (p = 0.004, Student T-test) which also showed significant decrease after the botulinum-toxin treatment (p = 0.033). Motor symptoms and pain in female patients did not correlate with the BAI score.

Discussion

In this cohort of 39 patients the only difference between the two groups concerning sex was higher initial BAI index in female patients compared to men, who also showed significant BAI score reduction after treatment in comparison to male subjects. Although the BAI is not recommended as a diagnostic tool to detect anxiety disorders, research data support the BAI reliability and validity as a tool to measure the severity of general anxiety in clinical and non-clinical populations; however, it fails to capture the unique characteristics of anxiety disorders that distinguish them from depressive disorders [31-33]. According to literature, anxiety and depression are significantly more often in patients with CD compared to healthy controls, and are also primary non-motor and premotor symptoms of cervical dystonia [19]. Our findings are consistent in prior research that show accented non-motor psychiatric symptoms in female patients compared to men [19]. The initial higher BAI scores in female did not correlate with the severity of motor symptoms both be-

fore and after treatment, suggesting that possible anxious disorder is not the sole result of social anxiety concerning patients motor state, but can very well be a separate entity of the disease itself that does not account for the severity of cervical dystonia.

A growing body of evidence supporting this premise are in the reports that show that anxiety and social anxiety severity vary by onset site of focal dystonia, and this variation is not explained by differences in pain and dystonia severity [34,35]. There are other facts suggesting psychiatric symptoms as an intrinsic factor for cervical dystonia-some genetic forms of dystonia (such as myoclonus dystonia with D4T11 mutation) show greater frequency of concomitant anxiety than in other forms of cervical dystonia without the mutation [36]. Also, some other illnesses bearing much greater stigma on overall appearance (such as alopecia) in comparison to motor symptoms in cervical dystonia paradoxically show much less occurrence of anxiety [37]. All these facts contribute to previously discussed new ideas in CD pathophysiology concerning lower GABA levels and sex differences. Since it was found that patients with dystonia presented an inverse association between the severity of depressive and anxiety symptoms and the availability of dopaminergic transporter in the left putamen suggesting striatal pathway dysfunction and that the majority of CD patients are older females that have shown to have lower GABA levels specific research towards gamma aminobutyric acid GABAergic function might be a new and exciting way of cervical dystonia pathogenesis research [25,26,38,39].

This study was the first Croatian study evaluating and correlating the motor and non-motor symptoms among sexes before and after botulinum toxin treatment in patients with focal cervical dystonia. The prevalence of cervical dystonia is 2 times higher in women than men, while both sexes show significant improvement of all symptoms after the botulinum-toxin treatment. Anxiety is significantly more expressed in female patients and does not correlate with the severity of motor symptoms. Considering higher incidence of female sex and non-motor symptoms such as anxiety that are more often found in CD patients which both can be linked to altered GABA levels, exploring neurotransmitter pathways in women suffering from cervical dystonia might bring new light to CD basic pathophysiology.

For now there is no answer to what measure anxiety appears as an intrinsic factor as to whereas it is a consequence of social anxiety concerning motor symptoms. Onset of psychiatric disturbances in patients with dystonia often precedes onset of motor symptoms suggesting that the pathophysiology of dystonia itself contributes to the genesis of psychiatric disturbances, but It is difficult to draw a clear line that dichotomizes the population between those with intrinsic and those with reactive psychopathology [40]. For the time being there are no official scales or questionnaires to asses psychiatric status along the motor status as it is in some other neurological conditions, for example such as Unified Parkinson Disease Rating Scale (UPDRS questionnaire) in Parkinson disease. What can be done for this particular group of patients would be to standardize the use of mood-assessing questionnaires within the initial physical examination when suspecting cervical dystonia to be able to start the treatment of possible psychiatric symptoms or illness timely and by doing so improving the quality of life within this group of patients.

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Conflict of interest

None to declare.

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