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Prevalence of non-motor symptoms and their association with quality of life in cervical dystonia

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Objectives: Non-motor symptoms (NMS) are commonly present along with motor impairment in patients with cervical dystonia (CD) and have a significant impact on health-related quality of life (HRQoL). However, the prevalence of NMS and their association with dystonia are still unclear. The aim of our study was to assess the prevalence of depression, anxiety, fatigue, apathy, pain, sleep problems, and excessive daytime sleepiness (EDS) in CD using different evaluation approaches and to explore their association with HRQoL relative to that of motor symptoms.

Materials and Methods: We enrolled 102 Slovak patients with CD. The severity of both motor and non-motor symptoms was assessed using validated scales. HRQoL was determined by the 36-item Short Form Health Survey (SF-36). Association of NMS with poor HRQoL was assessed using multiple regressions.

Results: The most frequent NMS in our sample were sleep impairment (67.3%), anxiety (65.5%), general and physical fatigue (57.5% and 52.9%, respectively), depression (47.1%), mental fatigue (31.4%), apathy (30.4%), reduced activity (29.4%), EDS (20.2%), and reduced motivation (18.6%). Univariate analysis showed that NMS, but not motor symptoms, were significantly linked to poor HRQoL, with EDS being most commonly associated with poor HRQoL, followed by disrupted sleep, depression, and fatigue.

Conclusions: The prevalence of NMS among patients with CD is high, and some NMS are strongly associated with poor HRQoL, while motor impairment was not associated with the severity of NMS or poor HRQoL. Actively diagnosing and treating NMS should therefore be a routine part of the clinical management of patients with CD.

KEYWORDS
anxiety, apathy, depression, dystonia, fatigue, non-motor, pain, sleep

1 | INTRODUCTION

Despite the purely motor-related definition of cervical dystonia (CD),[1] evidence is growing that non-motor symptoms (NMS) are frequently present in CD patients and have a significant impact on the health-related quality of life (HRQoL) of these patients.[2] Depression and anxiety in particular were reported to be associated with CD and may be an intrinsic part of the CD phenotype.[3] Neuropsychiatric

symptoms appear to be associated with poor HRQoL independently of the severity of motor symptoms.[4]

The intrinsic nature of other NMS, such as fatigue, sleep disturbances, and pain, commonly present in CD patients and their association with HRQoL are less certain.[5-7] Moreover, several NMS commonly associated with other basal ganglia disorders, such as apathy, have not yet been systematically studied in relevant cohorts of patients with CD.

Specific rating scales for evaluating NMS in CD, like the Dystonia Non-Motor Symptoms Questionnaire (DNMSQuest),[8] provide a simple self-reported overview of NMS prevalence burden, while symptom-specific scales, like Beck's Depression Inventory, assess only a single NMS, but in more detail, including symptom severity. Due to the limited research done on this topic thus far, it is not clear what the concordance is between these evaluation approaches and what the most important determinants of HRQoL in CD patients subjectively are.

Thus, the aim of our study was to assess the prevalence of depression, anxiety, fatigue, apathy, pain, sleep problems, and excessive daytime sleepiness (EDS) in a cross-sectional study of Slovak patients with CD and to explore the association of these NMS with HRQoL relative to that of motor symptoms.

2 | METHODS

2.1 | Participants and procedure

During the study period (2/2016-5/2018), we enrolled all consecutive patients with idiopathic CD from four Slovak specialized dystonia outpatient clinics, which serve as treatment centers for CD. Since we aimed to recruit a natural, non-biased cohort, we did not apply any exclusion criteria. Clinical diagnosis was made by a movement disorder specialist (VH, MSk, MKT). After this initial examination, patients were given the printed version of the questionnaires the same day to complete at home within one week, prior to the therapeutic effect of botulinum neurotoxin A (BoNT-A) injections, and were asked to return the questionnaires to the clinic. Written informed consent was obtained from all participants prior to the study. The study was approved by the local ethics committee (PJ Safarik University, Kosice, Slovakia, No. 13N/2015).

2.2 | Measures

2.2.1 | Motor symptoms

We evaluated the severity and disability of CD using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).[9] We also used the 7-point Clinical Global Impression Scale (CGI-S)[10] to evaluate the overall clinical severity of dystonia and also considered head tremor, since the TWSTRS does not include assessment of head tremor. In both scales, higher scores indicate more severe symptoms (all ranges shown in Table 1).

2.2.2 | Non-motor symptoms (NMS)

In order to assess the presence and severity of NMS, we used translated validated symptom-based scales for depression, anxiety, apathy, fatigue, sleep disturbances, and pain, as explained below.

Depressive and anxiety symptoms were evaluated using Beck's Depression Inventory-II (BDI-II)[11] and Beck's Anxiety Inventory (BAI),[12] respectively. Scores ≥ 14 on the BDI-II and ≥ 10 on the BAI indicated the presence of the respective NMS.

Apathy was measured using the 14-item Starkstein's Apathy Scale (SAS),[13] originally developed for patients with Parkinson's disease (PD) but also commonly used to assess apathy in other neurological conditions, including dystonia. Scores ≥ 14 define the presence of apathy.

Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI), a self-report 20-item instrument covering the dimensions of General Fatigue, Physical Fatigue, Reduced Activity, Reduced Motivation, and Mental Fatigue.[14] Although the original MFI does not come with recommended cutoff scores, in accordance with previously published studies,[15] we applied a cutoff score of ≥ 13 in each MFI domain to indicate the presence of fatigue.

Nocturnal sleep disturbances were measured using the Pittsburgh Sleep Quality Index (PSQI),[16] with scores ≥ 5 interpreted as impaired sleep quality. Daily sleep problems were evaluated with the Epworth Sleepiness Scale (ESS),[17] with scores ≥ 10 considered significant for excessive daytime sleepiness (EDS).

The presence of *pain* and its severity and impact on daily activities were assessed using the TWSTRS pain subscale (TWSTRS-pain).[9] It combines an analogue scale for pain (0 = no pain, 10 = worst possible pain due to CD), a duration factor, and disability due to pain.

Furthermore, we assessed the prevalence of NMS using the 14-item self-report questionnaire proposed by Klingelhoefer,[18] which was recently validated as the DNMSQuest,[8] to which we added one question regarding sexual problems. This additional question was included based on reported problems with sexual activities in patients with CD.[2] Patients answered "yes" or "no" on each item to mark the presence or absence of a particular NMS. We included this questionnaire in order to gain highly personalized insight into patients' perceived symptoms, not biased by the arbitrary cutoffs of standardized questionnaires mentioned above. We also asked patients to make their own list of the five most bothersome symptoms from the mentioned list of 15 NMS, where we added 4 motor symptoms relevant to CD (head tremor, abnormal position of head, limited range of head movements, and limitations in daily activities due to dystonia).

Health-Related Quality of Life (HRQoL) was evaluated using the 36-item Short Form Health Survey (SF-36), which is widely used in clinical practice and research.[19] Scores are computed for each domain separately, with lower scores indicating worse

TABLE 1 Clinical characteristics of the sample

Clinical characteristics of the sample (N = 102)			
Variable	**Mean (SD)**	**Median (range)**	**Range of the scale**
Age	55.6 (13.9)	56 (18-87)	
Gender male (%)—female (%)	26 (25.5%) - 76 (74.5%)		
Motor severity of dystonia			
CGI-S	4.2 (1.2)	4 (2-7)	0-7
TWSTRS severity subscale	16.4 (5.3)	16 (6-30)	0-35
Non-motor symptoms			
BDI-II	14.4 (10.6)	12 (0-42)	0-63
BAI	15.1 (10.3)	14 (0-49)	0-63
SAS	12.1 (6.8)	11 (1-30)	0-42
MFI—General Fatigue	13.4 (4.9)	14 (4-20)	4-20
MFI—Physical Fatigue	13.1 (4.7)	13 (4-20)	4-20
MFI—Reduced Activity	10.5 (4.2)	11 (4-20)	4-20
MFI—Reduced Motivation	8.5 (3.8)	8 (4-20)	4-20
MFI—Mental Fatigue	10.8 (4.3)	11 (4-20)	4-20
PSQI	6.4 (3.7)	5 (0-18)	0-21
ESS	6.6 (3.8)	6 (0-21)	0-24
TWSTRS pain subscale	7.3 (4.2)	8 (0-14)	0-20
Disability			
TWSTRS disability subscale	10.2 (4.5)	10 (1-20)	0-30
Health-related quality of life			
SF-36 Physical functioning	62.8 (26.9)	70 (0-100)	0-100
SF-36 Social functioning	60.1 (27.4)	62.5 (0-100)	0-100
SF-36 Role limitations physical functioning	40.2 (40.6)	25 (0-100)	0-100
SF-36 Role limitations emotional problems	63.7 (42.2)	100 (0-100)	0-100
SF-36 Mental health	58.3 (19.8)	60 (12-100)	0-100
SF-36 Vitality	46.3 (20.4)	45 (0-95)	0-100
SF-36 Bodily pain	50.7 (28.4)	45 (0-100)	0-100
SF-36 General health perceptions	44.2 (19.3)	45 (0-90)	0-100
SF-36 Expected health change	39.1 (24.8)	50 (0-100)	0-100
- SF-36 Physical Component Summary	39.5 (10.2)		
- SF-36 Mental Component Summary	41.1 (12.1)		

Note: Higher scores in the motor, non-motor, and disability scales indicate more severe symptoms. Lower scores in SF-36 domains are associated with decreased HRQoL

Abbreviations: SD, standard deviation, CGI-S, Clinical Global Impression Scale—Severity, TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale, BDI, Beck's Depression Inventory, BAI, Beck's Anxiety Inventory, SAS, Starkstein's Apathy Scale, MFI, Multidimensional Fatigue Inventory, PSQI, Pittsburgh Sleep Quality Index, ESS, Epworth Sleepiness Scale, SF-36, 36-item Short Form Health Survey.

HRQoL. Physically relevant items were converted into a single Physical Component Summary (PCS) item, and items related to emotions were used to compute a Mental Component Summary (MCS).

2.3 | Statistical analyses

First, we described the clinical characteristics of our sample, including the prevalence of NMS. Second, we assessed the correlation of the

TABLE 2 Reported non-motor symptoms in patients with cervical dystonia according to DNMSQuest

Reported non-motor symptoms in patients with cervical dystonia according to DNMSQuest (N = 93)	
Symptom	**Prevalence (%)**
Loss of self-confidence due to stigma of visible head/neck dystonia	65.6
Fatigue (tiredness) or lack of energy which limits daytime activities	61.3
Any walking difficulty or balance problem	58.1
Difficulties falling or staying asleep	57.0
Experience of light-headedness or dizziness	57.0
Feeling sad or depressed	50.5
Experience of unpleasant sensation, such as numbness, tingling, or pins and needles	46.2
Feeling not refreshed after an overnight sleep	41.9
Feeling nervous, worried, or frightened for no apparent reason	41.9
Dystonia affecting vision	35.5
Problems with or less interested in sexual activities	34.4
Pain not explained by other conditions	31.2
Difficulties while eating, such as chewing or swallowing	30.1
Flat moods without the normal "highs" and "lows"	28.0
Any speech problems	23.7

Note: Adopted according to Klingelhoefer et al 2014 (later validated as DNMSQuest by Klingelhoefer et al 2019) with the additional question on sexual problems.

severity of motor and non-motor symptoms with all the SF-36 subscales, including PCS and MCS. For the MCS and for some NMS, we found indications for non-normality of the variables. Because of that, for those instances we also computed Spearman's rank correlation coefficients, on top of Pearson's correlation coefficients. These showed differences between the two to be very small (maximum difference 6%), indicating no important impact of non-normality. Symptoms with a significant correlation to a HRQoL domains were added to the multiple linear regression model in order to evaluate their influence on HRQoL, which was performed in stepwise approach. Multiple imputation was used to handle missing values (3.05%), and all the subsequent analyses were performed on pooled data. Analyses were performed using IBM SPSS Statistics 25 for Windows (SPSS Statistics, IBM Corporation).

TABLE 3 Prevalence of non-motor symptoms based on symptom-specific scales and DNMSQuest

Prevalence of non-motor symptoms (NMS) based on symptom-specific scales and DNMSQuest					
Non-motor symptom	**Presence of NMS according to rating scale with applied cutoff (%)**		**Presence of NMS according to DNMSQuest (%)**	**Concordant result in both measures (%)**	**Pearson's chi-square significance**
Depression	BDI-II ≥ 14	47.1	50.5	70.9	<0.001
Anxiety	BAI ≥ 10	65.5	41.9	70.7	<0.001
Apathy	SAS ≥ 14	30.4	28.0	68.8	0.023
Fatigue	MFI—General Fatigue ≥ 13	57.5	61.3	73.9	<0.001
	MFI—Physical Fatigue ≥ 13	52.9	61.3	72.0	<0.001
	MFI—Reduced Activity ≥ 13	29.4	61.3	61.3	<0.001
	MFI—Reduced Motivation ≥ 13	18.6	61.3	45.1	0.501
	MFI—Mental Fatigue ≥ 13	31.4	61.3	59.1	0.002
Sleep disturbances	PSQI ≥ 5	67.3	57.0	81.6	<0.001
Excessive daytime sleepiness	ESS ≥ 10	20.2	-	-	-

Abbreviations: DNMSQuest, Dystonia Non-Motor Symptoms Questionnaire, BDI, Beck's Depression Inventory, BAI, Beck's Anxiety Inventory, SAS, Starkstein's Apathy Scale, MFI, Multidimensional Fatigue Inventory, PSQI, Pittsburgh Sleep Quality Index, ESS, Epworth Sleepiness Scale.

3 | RESULTS

3.1 | Clinical characteristics

We enrolled 102 patients (76 females: 74.5%) with CD into the study. The mean age of the sample was 55.6 ± 13.9 years. Thirty-nine patients (38.2%) suffered from dystonic head tremor. The mean age of dystonia onset was 44.9 ± 15.1 years, and the mean duration of the disease was 9.9 ± 8.9 years. Detailed clinical characteristics are displayed in Table 1. In addition, this table also shows the mean score of the determinants of HRQoL, including PCS and MCS. Almost half of the patients (46.1%) had a lifelong history of a referral to psychiatrist for any psychiatric diagnosis. Concomitant medication potentially influencing the NMS which was taken by our patients included benzodiazepines (33.3%), antidepressants (14.7%), neuroleptics (3.9%), and anticholinergics (4.9%). Excessive daytime sleepiness was slightly more frequent among patients using benzodiazepines (23.5% vs. 17.6%); similarly, apathy was more prevalent in this group (35.3% vs. 27.9%). However, the prevalence of general fatigue, depression, and anxiety did not significantly differ regarding the usage of benzodiazepines.

3.2 | Prevalence of non-motor symptoms

Perceived NMS according to the DNMSQuest are shown in Table 2. At least one NMS was reported by 94.6% of the patients and 67.7% complained of five or more NMS. The mean number of reported NMS was 6.6 ± 3.8 (range 0-15). The most frequent NMS in our sample was sleep impairment (67.3% in the PSQI and 56.3% in the DNMSQuest), followed by anxiety (65.5% in the BAI and 41.3% in the DNMSQuest), general and physical fatigue (57.5% and 52.9%, respectively, in MFI and 61.3% in the DNMSQuest), and depression (47.1% in BDI-II and 50.5% in the DNMSQuest). Apathy, according to SAS, was present in 30.4% of the patients compared to 28.0% as assessed by the DNMSQuest. The list of NMS with their prevalence and differences between the different assessment approaches is displayed in Table 3. The most bothersome NMS and motor symptoms are shown in Table 4.

3.3 | Association of HRQoL with NMS

Univariate analysis showed that HRQoL in patients with CD was correlated with depression, anxiety, apathy, fatigue, sleep impairment, excessive daytime sleepiness, pain, and disability. Motor symptoms, however, were not significantly linked to poor HRQoL (Table 5). To exclude the possibility that NMS independently correlate with HRQoL, in addition we performed the correlation of NMS and motor symptoms which did not show a significant association, except the score for pain which correlates with TWSTRS-severity (Table S1).

Multiple linear regression analysis showed that motor symptoms alone cannot significantly explain the variations in PCS (adjusted R^2-0.015, *P*-value 0.859 for TWSTRS-severity and 0.943 for CGI-S) or in MCS (adjusted R^2 0.031, *P*-value 0.103 for TWSTRS-severity and 0.160 for CGI-S). After additional inclusion of NMS into the linear regression analysis, this model was able to explain 53% of the variations in PCS ($P < .001$) and nearly 58% of the variations in MCS ($P < .001$).

Subsequent linear regression analysis took into consideration only those NMS that were significant in the previous model. Higher levels of fatigue and poor sleep quality were associated with worse physical HRQoL, as measured by PCS, while depression and excessive daytime sleepiness were associated with worse mental HRQoL, as measured by MCS, and also remained significant when controlled for gender and age. Among all the NMS, excessive daytime sleepiness (EDS) was most frequently associated

TABLE 4 Top 5 most bothersome symptoms—motor and NMS (N = 88)

Symptom	Proportion of patients who marked it as top 5 most bothersome symptoms (%)
Tremors, twitching	59.1
Loss of self-confidence due to stigma of visible head/neck dystonia	56.8
Fatigue (tiredness) or lack of energy which limits daytime activities	43.2
Difficulties falling or staying asleep	37.5
Change of head position	36.4
Any walking difficulty or balance problem	35.2
Experience of light-headedness or dizziness	33.0
Feeling nervous, worried, or frightened for no apparent reason	25.0
Limitation of daily activities (due to the limited movements in dystonia)	23.9
Experience of unpleasant sensation, such as numbness, tingling, or pins and needles	21.6
Feeling sad or depressed	20.5
Pain not explained by other conditions	19.3
Limited range of movement of the head	18.2
Dystonia affecting vision	15.9
Feeling not refreshed after an overnight sleep	13.6
Difficulties while eating, such as chewing or swallowing	10.2
Problems with or less interested in sexual activities	8.0
Any speech problems	8.0
Flat moods without the normal "highs" and "lows"	3.4

Notes: bold = motor symptom.

TABLE 5 Correlations between the domains of health-related quality of life and clinical variables

Correlations between the domains of Health-related Quality of Life and clinical variables											
	Correlation coefficient										
Variable	PF	SF	RLP	RLE	MH	Vitality	Pain	GHP	EHC	PCS	MCS
Demographic characteristics											
Age	-0.281**	0.135	-0.014	0.023	0.044	0.043	-0.075	-0.070	0.069	-0.195*	0.132
Gender	0.329**	0.029	0.072	0.112	0.046	0.274**	0.114	0.019	0.030	0.202*	0.053
Motor severity of dystonia											
CGI-S	-0.001	-0.072	0.068	0.062	0.120	0.074	0.020	-0.142	-0.003	-0.017	0.061
TWSTRS severity subscale	-0.055	-0.178	-0.064	-0.078	-0.064	-0.015	-0.031	-0.110	0.011	-0.019	-0.100
Non-motor scores											
BDI-II	-0.442**	-0.651**	-0.426**	-0.496**	-0.759**	-0.756**	-0.624**	-0.502**	-0.409**	-0.442**	-0.703**
BAI	-0.428**	-0.551**	-0.421**	-0.511**	-0.626**	-0.621**	-0.567**	-0.443**	-0.375**	-0.418**	-0.621**
SAS	-0.269**	-0.308**	-0.181	-0.302**	-0.526**	-0.480**	-0.289**	-0.406**	-0.114	-0.238*	-0.449**
MFI—General Fatigue	-0.597**	-0.486**	-0.444**	-0.334**	-0.422**	-0.694**	-0.595**	-0.516**	-0.288**	-0.618**	-0.385**
MFI—Physical Fatigue	-0.617**	-0.512**	-0.443**	-0.358**	-0.470**	-0.701**	-0.561**	-0.566**	-0.334**	-0.608**	-0.423**
MFI—Reduced Activity	-0.533**	-0.482**	-0.425**	-0.494**	-0.561**	-0.676**	-0.564**	-0.526**	-0.303**	-0.517**	-0.543**
MFI—Reduced Motivation	-0.349**	-0.344**	-0.314**	-0.349**	-0.515**	-0.560**	-0.353**	-0.389**	-0.144	-0.320**	-0.453**
MFI—Mental Fatigue	-0.398**	-0.433**	-0.380**	-0.456**	-0.609**	-0.661**	-0.478**	-0.403**	-0.263**	-0.368**	-0.575**
PSQI	-0.503**	-0.460**	-0.501**	-0.375**	-0.496**	-0.593**	-0.658**	-0.470**	-0.383**	-0.586**	-0.424**
ESS	-0.331**	-0.391**	-0.375**	-0.309**	-0.397**	-0.399**	-0.319**	-0.314**	-0.249*	-0.324**	-0.394**
TWSTRS pain subscale	-0.232*	-0.317*	-0.215	-0.063	-0.234	-0.404*	-0.397**	-0.164	-0.081	-0.299*	-0.216
Disability											
TWSTRS disability subscale	-0.145	-0.440**	-0.222*	-0.142	-0.376**	-0.405**	-0.419**	-0.322**	-0.211*	-0.258**	-0.348**

Abbreviations: CGI-S, Clinical Global Impression Scale—Severity, TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale, BDI, Beck's Depression Inventory, BAI, Beck's Anxiety Inventory, SAS, Starkstein's Apathy Scale, MFI, Multidimensional Fatigue Inventory, PSQI, Pittsburgh Sleep Quality Index, ESS, Epworth Sleepiness Scale, PF, physical functioning, SF, social functioning, RLP, role limitation—physical, RLE, role limitation—emotional, MH, mental health, GHP, general health perception, EHC, expected health change, PCS, Physical Component Summary, MCS, Mental Component Summary.

*$P < .05$.

**$P < .01$.

with worse HRQoL, followed by disrupted sleep, depression, and fatigue (Table 6).

4 | DISCUSSION

This study showed a considerable prevalence of NMS in patients with CD. The complex spectrum of NMS, including apathy, has not been evaluated in previous studies, especially in larger CD samples. Besides subjective qualitative perception of NMS,[8] we also assessed the severity of NMS using symptom-specific questionnaires.[11-14,16,17] Among these NMS, EDS, poor sleep, depression, and fatigue seem to be especially important determinants of HRQoL in CD. In contrast, motor disability was not associated with NMS severity or impaired HRQoL.

4.1 | Prevalence of NMS

We found disrupted sleep to be the most common non-motor complaint in our cohort, with a prevalence of 67.3%, which also corresponds to "difficulties falling or staying asleep" in the DNMSQuest.

For 37.5%, it ranks among the five most bothersome symptoms. An increased proportion of sleep disturbances in patients with CD has been confirmed by several studies.[7,20] Disrupted sleep in dystonia is not clearly explained yet, and the possible link between poor sleep and dystonia also involves a hypothesis that both disorders may be due to the same pathological mechanisms of basal ganglia including dopaminergic dysregulation.[21] Poor sleep quality may lead to "a feeling of not being refreshed after overnight sleep," which was perceived by 41.9% of our sample according to the DNMSQuest. Our patients also commonly suffered from EDS (20.2%), which together with fatigue may be a consequence of sleep problems. Although fatigue is a very frequent symptom associated with chronic neurological diseases, including PD[22] and multiple sclerosis,[23] its prevalence is higher than we would expect based solely on age or disability due to the disease. In our sample, 70.6% of patients reached the cutoff score for fatigue in at least one MFI subscale. In addition, 61.3% of our patients reported limitation due to fatigue in the DNMSQuest, and in 43.2%, fatigue was included among the five most bothersome symptoms. The reported prevalence of fatigue in CD ranges from 46%[7] to 64%.[6] Based on the prevalence and self-reported burden, fatigue seems to be among the most relevant NMS in CD.

Neuropsychiatric symptoms were found to be more frequent in CD compared to healthy controls.[2] In our sample, anxiety was the second most common NMS (65.5% prevalence). Such a high prevalence of anxiety in CD has not been previously reported, since it commonly ranges from 21% to 42%,[2,24] which better corresponds with "a feeling of being nervous, worried or frightened for no apparent reason" in the DNMSQuest in 41.9% of our participants. The difference in reported studies may be due to different assessment approaches (clinical examination according to DSM-IV criteria vs. different questionnaires). Levels of anxiety in our group were higher than those among patients with multiple sclerosis (27%) living in the same region.[25] Similarly, depression was also more common in

TABLE 6 Determinants of decreased health-related quality of life for individual SF-36 domains and component summaries in patients with cervical dystonia

Determinants of decreased health-related quality of life for individual SF-36 domains and component summaries in patients with cervical dystonia

SF-36 domain	Determinant(s)	Adjusted R^2	B	β	*P*-value
Physical functioning	PSQI	0.294	-3.960	-0.549	< 0.001
Social functioning	BDI-II	0.470	-1.531	-0.594	< 0.001
	ESS		-1.718	-0.241	0.001
Role limitations—physical functioning	ESS	0.138	-4.060	-0.383	< 0.001
Role limitations—emotional problems	ESS	0.114	-3.854	-0.350	< 0.001
Mental health	BDI-II	0.587	-1.293	-0.694	< 0.001
	ESS		-1.072	-0.208	0.002
Vitality	BDI-II	0.610	-1.336	-0.695	< 0.001
	ESS		-1.250	-0.235	< 0.001
Bodily pain	MFI-GF	0.461	-2.307	-0.397	< 0.001
	PSQI		-2.913	-0.382	< 0.001
General health perceptions	MFI-PF	0.326	-2.365	-0.577	< 0.001
Expected health change	PSQI	0.142	-2.575	-0.387	< 0.001
Physical Component Summary	MFI-GF	0.496	-0.996	-0.479	< 0.001
	PSQI		-0.888	-0.325	< 0.001
Mental Component Summary	BDI-II	0.575	-0.780	-0.686	< 0.001
	ESS		-0.654	-0.208	0.002

Note: Linear regression modeling revealed only particular non-motor symptoms as predictors of the worsened scores in SF-36 domains, whereas models which included motor symptoms alone were insignificant (and are not displayed here).

Abbreviations: SF-36, 36-item Short Form Health Survey, R^2, squared correlation coefficient, B, unstandardized coefficient, β, standardized coefficient, BDI, Beck's Depression Inventory, MFI-GF, Multidimensional Fatigue Inventory—General Fatigue, PSQI, Pittsburgh Sleep Quality Index, ESS, Epworth Sleepiness Scale.

our sample (47.1%) compared to Slovak multiple sclerosis patients (8.7%)[25] but lower than that in Slovak PD patients.[22] Furthermore, 50.5% of our group reported "feeling sad or depressed" in the DNMSQuest, which is in line with the above-mentioned prevalence. The reported prevalence of depression in CD ranges from 25%[20] to 47%.[26] This difference in prevalence may be caused by different exclusion criteria applied during patient recruitment. Also, the fact that patients come from a particular area (Slovakia) may play a role as the perception of particular NMS may differ among various populations. CD patients may suffer from higher levels of anxiety and depression due to the visible stigma of the disease. In that case, we would expect significant correlation between motor disability and severity of these neuropsychiatric symptoms, which was, however, not found in our study. This finding supports the assumption that neuropsychiatric symptoms are an intrinsic part of dystonia's phenotype and are independent of motor symptoms.

To our best knowledge, no systematic assessment of apathy in patients with CD has ever been performed in larger cohorts. According to our findings, 30.4% of patients with CD suffered from apathy. In the small study of Louis,[27] higher levels of apathy compared to healthy controls were reported in CD (N = 12), PD, and essential tremor. The prevalence of apathy in that study, which included 20 patients with dystonia, was 20%.[28] For comparison, patients with PD suffered from more severe apathy in both studies,[27,28] and apathy was linked with cognitive decline in PD.[22] A Brazilian study[29] that included 28 patients with CD showed a threefold higher risk of apathy compared to controls. It seems that apathy is a common NMS in CD; however, its association with poor HRQoL is uncertain and deserves further investigation together with other cognitive functions.

Pain associated with CD was reported in 31.2% of cases according to the DNMSQuest. In comparison, data from a multicenter, prospective, observational "CD PROBE" registry[30] suggest a much higher prevalence (nearly 90%) of pain in CD. This discrepancy is probably caused by using different tools to assess pain and favors a single-item question on the current level of pain (range 0-10) over a complex question on the presence of pain, as used in this study. Nearly 90% of our patients also reported pain when evaluating the presence of any pain (including pain not associated with CD) according to the SF-36 Pain subscale.

Comparison of a scale-based assessment of NMS with their evaluation by a single question according to the DNMSQuest shows the highest concordance for disrupted sleep (81.6% of congruent results in the PSQI and the DNMSQuest). Considerable concordance was also observed when evaluating depression (70.9%), anxiety (70.7%), general and physical fatigue (73.9% and 72.0%, respectively), and apathy (68.8%). Despite the relatively high concordance of both approaches, there were still 18%-28% of patients whose self-estimated presence/absence of a particular NMS in the DNMSQuest was incongruent with the result of the scale specific to that NMS. Simultaneous screening for NMS by both approaches may increase the detection rate, however, at the cost of increased clinical effort. This elicits the need for a useful questionnaire capable of screening for CD-related NMS while simultaneously evaluating their severity.

Our study reinforces previous observations that NMS are frequent in CD.[2,6] Given that CD is a disorder of basal ganglia and their circuits, which also have projections into the limbic system, it is not unexpected that various non-motor functions may be affected in patients with CD. Moreover, alterations in the serotoninergic system are considered in the pathogenesis of dystonia, and both motor and non-motor symptoms of dystonia show significant relationship with altered serotoninergic activity in raphe nuclei, the caudate nucleus, and the hippocampus.[31]

4.2 | Determinants of CD-related QoL

Our study confirmed previous observations[2,4,6] that HRQoL is determined mainly by NMS and not by motor impairment. In this regard, sleep problems, depression, and fatigue seem to be important determinants of poor HRQoL.

Regression analysis revealed EDS, disrupted sleep, depression, and fatigue to be associated with worsened HRQoL. A model with MFI-GF and PSQI explains almost half (49.6%) of the variation in PCS, and depression together with EDS is responsible for 57.5% of the variation in MCS. Physical well-being in patients with dystonia is hence mainly determined by sleep quality and perceived general fatigue, while mental well-being is negatively influenced by depression and EDS.

Compared to other studies[4,6] focused on identifying associations of poor HRQoL with NMS in CD, we found that despite the considerable prevalence of anxiety, apathy, and pain, these NMS were not independently associated with worsened HRQoL. Sleep problems (worsened sleep quality, EDS) were particularly often associated with poor HRQoL in our study also when controlled for other NMS—including depression—which should bring more attention to sleep problems when managing patients with CD.

4.3 | Strengths and limitations

This study describes the prevalence of NMS in CD and the impact of NMS on HRQoL on a larger sample of patients. Besides depression and anxiety, we also took into consideration the effects of fatigue, apathy, pain, and sleep problems, which has never been done systematically in larger cohorts. Moreover, we compared two different approaches for evaluating the presence of NMS: symptom-specific questionnaires versus single-item questions from the DNMSQuest. However, we do not have data whether these NMS preceded the onset of motor manifestation of CD or whether they developed during the course of the disease. Also, the fact that almost half of the patients had a lifelong history of a referral to psychiatrist for any psychiatric diagnosis brings further uncertainty into the role of at least some NMS in CD, which may be clarified only in prospective studies.

The main limitation of our study is the absence of a control group; however, we tried to compare our study to similar studies on MS and PD in the same population. Another possible bias may

arise from the current treatment strategy of CD, as the application of BoNT injections targets mostly motor impairment, with uncertain effects on NMS, with the exception of pain. Hence, NMS may represent a larger burden for the patient than a well-treated motor disability. We tried to minimize this possible bias by scoring patients 12 weeks after their last BoNT administration, when the effect of BoNT has generally vanished. Although our study brings an overview of many frequently reported NMS in CD, we did not screen for obsessive-compulsive disorder and cognitive dysfunction which were reported among patients with various forms of dystonia.[32-36]

4.4 | Conclusions and implications

NMS are frequent among patients with CD, and their burden is higher than the disability caused by motor impairment. Active screening for NMS and subsequent treatment should be an integral part of clinical management of CD in order to improve patients' well-being. Screening for depression, fatigue, and sleep problems is particularly useful, since these NMS determined worse HRQoL in our sample. Additional studies with control groups should be conducted to better understand the higher prevalence of NMS among patients with CD. Future studies should focus on the pathophysiology of CD-related NMS to better understand the origin and contribution of NMS to the overall clinical picture of the disease.

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CONFLICT OF INTEREST

Authors do not have any conflicts of interest relevant to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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