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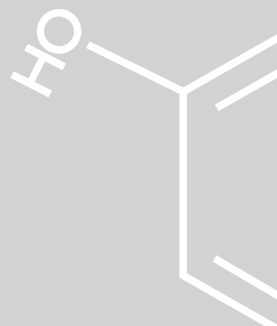
CHAPTER 4

The frequency and self-perceived impact on daily life of motor and non-motor symptoms in cervical dystonia

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Submitted.

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ABSTRACT

Background: Evidence suggest that non-motor symptoms (NMS) are the most important predictors of a decreased health-related quality of life (HR-QoL) in cervical dystonia (CD) patients. In this study, we evaluate a NMS screening list and examine the influence of motor and NMS on HR-QoL.

Methods: In forty CD patients the frequency of NMS was evaluated using an extended NMS-questionnaire [1]. Furthermore, patients composed a list of their five most burdensome motor and NMS and scored the severity of predefined symptoms. HR-QoL was examined with the RAND-36.

Results: 38 out of 40 patients experienced NMS (median number of NMS: 6.5, range 0-13, maximum 15). The self-perceived most burdensome symptoms were tremor/jerks, pain, sleep disturbances, daily-life limitations and fatigue. Also, of the predefined symptom list, tremor and fatigue were found most disturbing. All domains of HR-QoL were significantly influenced by several NMS, while motor symptoms only had a small influence on the domain physical functioning.

Conclusion: Our findings highlight the impact of NMS on HR-QoL and emphasize the importance of a standardized validated NMS-questionnaire for dystonia. This would enable to monitor the effect of motor and NMS treatment on an individual basis and improve treatment options.

INTRODUCTION

Cervical dystonia (CD) is a hyperkinetic movement disorder characterized by sustained or intermittent contractions of the cervical musculature, leading to abnormal head postures. Growing evidence suggests that the phenotype of CD also includes important non-motor symptoms (NMS), with psychiatric co-morbidity, pain, sensory abnormalities, sleep disturbances and fatigue most frequently described [2,3]. Importantly, these NMS are important predictors of a decreased health-related quality of life (HR-QoL) in CD [4]. It is acknowledged that Parkinson's disease patients have both motor- and NMS [5] with a major impact on HR-QoL. Similar to Parkinson's disease it is likely that in dystonia motor and NMS share common pathophysiological mechanisms. In Parkinson, NMS rating scales have already been developed over the last few years [6,7].

Recently, Klingelhofer et al. examined the frequency of NMS in CD patients, using a list of NMS derived from the NMS Questionnaire validated in Parkinson's disease [1,6]. In CD, 95% of patients experienced NMS. However, this study did not include the self-perceived impact of motor and NMS on daily life. Short lists of complaints in daily life determined by the patients themselves can be a good tool in clinical practice to focus on the most burdensome complaints [6].

In our study, we investigated the frequency of NMS by using an extended version of the NMS rating scale for CD patients as proposed by Klingelhofer et al [1]. We aimed to highlight a limited number of highly frequent NMS, which could be easily screened for in daily practice. In addition, we assessed self-perceived severity and impact of both motor symptoms and NMS on HR-QoL.

METHODS

Subjects

Forty patients (mean age 54.1 years, range 20-80 years) with a clinically diagnosed idiopathic CD were included. Thirty-seven of these patients were treated with botulinum toxin. Exclusion criteria were: onset before 18yr, treatment with DBS and other relevant neurological co-morbidity. Additionally, patients using antidepressant/serotonergic medication were excluded (n=8), because all subjects also participated in a study on psychiatric co-morbidity [8]. Patients were included via several botulinum toxin clinics and via the dystonia patient association. Informed consent was obtained from all participants and the study was approved by the local ethics committee.

NMS assessment

We assessed the frequency of NMS using the NMS list as proposed by Klingelhofer et al [1], with additionally a question about sexual problems (see table 1). Furthermore, patients

were asked to compose a list of their five most burdensome complaints, either motor complaints or NMS. To make this top five, patients were asked to choose symptoms from the NMS list as provided in table 1, supplemented with several motor symptom options (See also supplementary table 1). In addition, based on literature in combination with our experience, patients were asked to score the severity of symptoms with a high impact on HR-QoL on a scale from zero (no complaints) to ten (severe complaints). These symptoms included 'tremor/jerks', 'sad or depressed feeling', 'feeling nervous, worried or frightened for no apparent reason', 'sleep disturbances', 'fatigue', and 'pain not explained by other conditions'. HR-QoL was assessed with the RAND-36 item Health Survey (RAND-36) [9], consisting of nine domains of both physical and mental health. With the RAND-36 instead of the CDQ we will be able to compare our results with other forms of dystonia, which we would like to include in future studies.

Motor assessment

Motor assessment was performed using a systematic video protocol. If patients were treated with botulinum toxin, neurological assessment was performed between two weeks prior to or one week after the treatment (based on the individual treatment response time), in order to obtain the least influenced dystonia motor score. We scored CD severity with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [10]. Because the TWSTRS does not include the severity of jerks and tremor, jerks-tremor was separately scored by using the Clinical Global Impression Scale: CGI-S jerks-tremor (raising from zero (no complaints) to seven (severe complaints) [11]. The motor scores were independently scored by two experts (MS, VH, for further details see Smit et al. [8]) and revealed good (>0.85) intraclass correlation coefficients.

Statistical analysis

Statistical analysis was performed using PASW Statistics 22 for Windows (SPSS Statistics, Chicago IL, USA), and differences were considered significant at $p < 0.05$. To calculate the correlation between the number of NMS and clinical characteristics, we used the Spearman's rho test. For the point-biserial correlation between discrete dichotomous variables and HR-QoL domains, we used the Pearson's r test.

RESULTS

Dystonia characteristics

Forty CD patients were included (29 females, 11 males) with a mean age at onset of CD at 41.1yr (SD=11.81) and a mean disease duration of 13.1yr (SD=11.2). The mean total TWSTRS score was 33.31 (SD=12.91) (subscores TWSTRS: severity: 16.03 (SD=4.64), disability: 9.93 (SD=5.51), pain: 7.34 (SD=6.23)) and the mean CGI-S jerks-tremor score was 2.40 (SD=1.32).

Frequency of NMS and self-perceived impact

The frequency of the NMS is shown in table 1. In total, 38 out of 40 patients (95%) experienced at least one NMS (median number of NMS 6.5, range 0-13), while 25 (62.5%) experienced five (out of 15) or more NMS. Fatigue (76.3%) and pain (71.8%) were most frequently reported.

The individual top five of the most burdensome complaints, which could consist of both motor and NMS, is shown in table 2. Twenty-six patients completed the top five list; 14 patients only filled in four or less complaints (median number 2.5). The most frequently mentioned complaints were: tremor/jerks (23 times), pain (20 times), fatigue (19 times), sleep disturbances (18 times) and limitations in daily life (15 times) (See supplementary table 1 for a complete overview).

Severity of six predefined motor and NMS was rated by the patients on a scale from zero to ten. With a median score of 7, tremor (interquartile range 6.25 – 8) and fatigue (interquartile range 3.25 – 8) were rated as most severe complaints. The other symptoms showed median scores between 2.5 and 6.

Besides the list of NMS as provided in table 1, patients were asked if they experienced complaints which were not mentioned. Concentration problems were mentioned by two patients, and three patients experienced stress due to reactions from the environment and due to the inability to function appropriately at work.

Table 1
Frequency of non-motor symptoms in cervical dystonia patients

Non-Motor Symptom	Frequency
Fatigue or lack of energy which limits daytime activities	76.3%
Pain, not explained by other conditions	71.8%
Difficulties falling or staying asleep	62.5%
Loss of self-confidence due to stigma of visible head/neck dystonia	55.3%
Feeling not refreshed after an overnight sleep	51.3%
Any walking difficulty or balance problem	48.7%
Feeling sad or depressed	42.5%
Feeling nervous, worried or frightened for no apparent reason	36.8%
Dystonia affecting vision	35.9%
Problems with or less interested in sexual activities	34.2%
Experience of light headedness or dizziness	33.3%
Flat moods without the normal 'highs' and 'lows'	30.8%
Experience of unpleasant sensation such as numbness, tingling or pins and needles	30.8%
Any speech problems	26.7%
Difficulties while eating such as chewing or swallowing	25.6%

Table 2
Top 5 rating of most burdensome complaints

Symptom	Top 5 rating					Total	Mean
	1	2	3	4	5		
1. Tremor/jerks	13	4	2	2	2	23	1.96
2. Pain, not explained by other conditions	4	5	4	4	3	20	2.85
3. Difficulties falling or staying asleep	2	4	7	3	2	18	2.94
4. Fatigue or lack of energy which limits daytime activities	1	3	5	7	3	19	3.42
5. Limitations in daily activities	1	3	3	4	4	15	3.47

The data represent the number of patients who listed the symptom at the corresponding position in the top five. The top five is constituted of the five most frequent complaints, in order of the mean score.

Supplementary Table 1
Overview of all symptoms in the top 5 rating

Symptom	Top 5 rating					Total	Mean	Final top 5
	1	2	3	4	5			
Change of head position	2	3		1		6	2.00	
Tremor/jerks	13	4	2	2	2	23	1.96	1
Limited range of movement of the head	6	3	3		1	13	2.00	
Any walking difficulty or balance problem	2	1	3		2	8	2.88	
Experience of light headedness or dizziness	2		1	1		4	2.25	
Pain, not explained by other conditions	4	5	4	4	3	20	2.85	2
Loss of self-confidence due to stigma of visible head/ neck dystonia	1	5	2	2	1	11	2.73	
Feeling sad or depressed				1	2	3	4.67	
Flat moods without the normal 'highs' and 'lows'								
Feeling nervous, worried or frightened for no apparent reason		1	2	1	2	6	3.67	
Problems with or less interested in sexual activities		1			1	2	3.5	
Limitations in daily activities	1	3	3	4	4	15	3.47	5
Difficulties falling or staying asleep	2	4	7	3	2	18	2.94	3
Fatigue or lack of energy which limits daytime activities	1	3	5	7	3	19	3.42	4
Feeling not refreshed after an overnight sleep				2	2	4	4.5	
Experience of unpleasant sensation such as numbness, tingling or pins and needles			1		1	2	4	
Difficulties while eating such as chewing or swallowing	1	1		1		3	2.33	
Dystonia affecting vision	1					1	1	
Any speech problems	1				1	2	3	

The data represent the number of patients who listed this symptom at the corresponding position in the top five. The final top five is constituted of the five most frequent complaints, in order of the mean score.

Correlation between motor severity, non-motor symptoms and HR-QoL

The total number of NMS did not show a significant correlation with the TWSTRS severity scale ($r_s = -.07$, $p = 0.67$) or the CGI-S jerks-tremor scale ($r_s = .30$, $p = 0.06$). Also age ($r_s = -.29$, $p = 0.07$), gender ($r_s = .18$, $p = 0.26$) and disease duration ($r_s = -.07$, $p = 0.67$) did not show a significant correlation with the total number of NMS.

Looking at the correlations between motor characteristics and the individual NMS, the TWSTRS motor severity scale showed a significant correlation with a flattened affect ($r_{pb} = -.40$, $p = 0.01$), and the CGI-S jerks/tremor scale showed a significant correlation with 'loss of self-confidence or feeling embarrassed' ($r_{pb} = .54$, $p < 0.01$) and with 'feeling nervous, worried or frightened for no apparent reason' ($r_{pb} = .47$, $p < 0.01$).

To examine which symptoms were the most important contributors to a decreased quality of life (see Supp. table 2 for an overview of RAND-36 scores), we performed a univariate analysis with both motor and NMS. Besides a significant influence of limited movement on the domain physical functioning ($r_{pb} = -.39$, $p = 0.01$), only NMS significantly influenced the nine domains of HR-QoL (Table 3). The NMS feeling 'not refreshed after an overnight sleep' was most often associated with a decreased HR-QoL, affecting seven out of nine domains. Other NMS that were frequently associated with a decreased HR-QoL were 'fatigue or lack of energy which limits daytime activities' (4 out of 9), 'any walking difficulty or balance problem' (3 out of 9), 'feeling sad or depressed' (3 out of 9), 'problems with or less interested in sexual activities' (3 out of 9), 'experience of light headedness or dizziness' (3 out of 9) and 'experience of unpleasant sensation such as numbness, tingling or pins and needles' (3 out of 9)

Supplementary table 2

Mean values (standard deviation) of the nine domains of HR-QoL in CD patients.

Physical functioning	72.6 (21.0)
Social functioning	69.9 (20.3)
Role limitations physical	50.0 (42.7)
Role limitations mental	77.7 (37.3)
Mental health	71.1 (13.9)
Vitality	55.0 (17.0)
Pain	64.5 (21.8)
General health	58.4 (18.6)
Health change	48.6 (18.9)

Table 3

Univariate analysis between the nine domains of HR-QoL and motor- and non-motor symptoms

	PF	SF	RLP	RLE	MH	V	P	GHP	EHC
Motor symptoms									
Dystonic posturing	,151	-,002	,041	-,076	,069	,089	,012	,031	-,083
Tremor/jerks	-,060	,006	-,041	,065	-,040	-,084	,010	-,163	-,291
Limited movement	-,389*	-,029	-,189	-,080	,033	-,038	-,219	-,082	-,132
Non-motor symptoms									
Fatigue or lack of energy which limits daytime activities	-,433**	-,230	-,407*	-,198	-,258	-,292	-,470**	-,339*	-,063
Pain, not explained by other conditions	-,443**	-,227	-,292	-,259	-,239	-,283	-,470**	-,232	-,273
Difficulties falling or staying asleep	-,226	-,013	-,245	-,201	-,082	-,062	-,438**	-,223	,164
Loss of self-confidence due to stigma of visible head/neck dystonia	-,052	-,199	,000	,169	-,219	-,089	,119	-,052	,146
Feeling not refreshed after an overnight sleep	-,339*	-,451**	-,549**	-,427**	-,523**	-,612**	-,504**	-,295	-,248
Any walking difficulty or balance problem	-,505**	-,308	-,306	-,218	-,186	-,189	-,386*	-,326*	-,100
Feeling sad or depressed	-,219	-,595**	-,240	-,211	-,516**	-,482**	-,157	-,131	-,018
Feeling nervous, worried or frightened for no apparent reason	-,067	-,136	-,181	-,093	-,287	-,095	-,014	-,116	-,060
Dystonia affecting vision	-,304	-,195	-,264	-,212	-,254	-,278	-,232	-,340*	,011
Problems with or less interested in sexual activities	-,404*	-,123	-,218	-,378*	-,265	-,199	-,348*	-,075	-,067
Experience of light headedness or dizziness	-,283	-,333*	-,238	-,199	-,423**	-,421**	-,310	-,259	-,044
Flat moods without the normal 'highs' and 'lows'	-,038	-,300	-,145	-,138	-,318*	-,208	-,013	-,146	-,167
Experience of unpleasant sensation such as numbness, tingling or pins and needles	-,382*	-,440**	-,178	-,089	-,286	-,355**	-,301	-,298	-,152
Any speech problems	-,073	-,044	-,158	-,019	-,092	-,219	-,206	-,280	-,034
Difficulties while eating such as chewing or swallowing	-,096	-,387*	,053	-,007	-,359*	-,307	,051	,017	-,030

Data shown as correlation coefficient. PF = physical functioning. SF = social functioning. RLP = role limitation physical. RLE = role limitation emotional. MH = mental health. V = vitality. P = pain. GHP = general health perception. EHC = expected health change. *p<0.05, **p<0.01.

DISCUSSION

In this study, we showed that 95% of the CD patients experienced at least one and 62.5% at least five NMS, which is in accordance with the frequency described by Klingelhofer et al. [1]. Notably, because of the exclusion of subjects using psychoactive drugs, the number of NMS found in our study is likely an underestimation. The NMS pain was present in 71.8% of our participants, which is almost equal to the frequency found in other studies [3,12]. However, Klingelhofer et al found a lower frequency of 43.1% [1]. The cause of this difference is unclear, but could possibly be caused by different therapeutic approaches of pain or a different timing of questioning in relation to botulinum toxin therapy in CD patients.

The second aim of the study was to examine which complaints are experienced as most burdensome, rather than only highly frequent. The self-perceived top five of most burdensome complaints revealed three NMS, namely pain, sleep disturbances and fatigue. A high burden of these symptoms was confirmed in the rating of predefined symptoms, especially fatigue. These results highlight a limited number of NMS with a high impact on patient's life that could easily be screened for in daily practice. Moreover, it emphasizes the need not only to develop a short screening list for NMS for use in daily practice, but also to develop a method to quantify NMS in dystonia patients like the NMSS in Parkinson's disease [7].

In contrast to Klingelhofer et al. [1], we did not find a significant correlation between the number of NMS and motor severity. This difference could have been caused by different rating tools for measuring motor severity. In our study, we used specific cervical dystonia rating scales instead of a general dystonia rating scale. Our results even more highlight the importance of awareness for NMS in all CD patients, since also patients with mild dystonia could have a variety of NMS. Moreover, the need for screening of NMS in daily practice is emphasized by a significant influence of NMS on HR-QoL, while we did not find a significant correlation between motor severity and HR-QoL.

In conclusion, we replicated the high frequency of NMS as previously described [1]. Similar to Parkinson's disease, NMS in CD have long been underrecognized and undertreated, while they have a major impact on HR-QoL [4]. Our findings emphasize the importance of a validated short NMS questionnaire, in order to adjust treatment on an individual basis with attention for individual perceptions and to monitor the effect of motor and NMS treatment.

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