university of groningen

University Medical Center Groningen

University of Groningen

Motor and non-motor symptoms in cervical dystonia

Smit, Marenka

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Smit, M. (2017). *Motor and non-motor symptoms in cervical dystonia: a serotonergic perspective*. Rijksuniversiteit Groningen.

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 27-09-2021

CHAPTER 3

3

Fatigue, sleep disturbances and their influence on quality of life in cervical dystonia patients

M Smit
ASJ Kamphuis
AL Bartels
V Han
RE Stewart
I Zijdewind
MA Tijssen

Movement disorders clinical practice. 2016.

ABSTRACT

Background: Non-motor symptoms (NMS) are highly prevalent in cervical dystonia (CD). In general, fatigue and sleep are important NMS determining a decreased health-related quality of life (HR-QoL), but their influence in CD is unknown.

Objectives: We systematically investigated fatigue, excessive daytime sleepiness (EDS) and sleep quality in CD patients and controls and assessed the influence of psychiatric co-morbidity, pain and dystonia motor severity. Moreover, we examined the predictors of HR-QoL.

Methods: We included 44 CD patients and 43 matched controls. Fatigue, EDS and sleep quality were assessed with quantitative questionnaires and corrected for depression and anxiety using ANCOVA. We scored motor severity with the TWSTRS and CGI-S jerks/tremor scale and assessed whether motor characteristics could explain an additional part of the variation in fatigue and sleep-related measures. HR-QoL was determined with the RAND-36 item Health Survey, predictors of HR-QoL were assessed using multiple regression.

Results: Fatigue scores were increased independently from psychiatric co-morbidity (4.0 vs. 2.7, $p<0.01$), while EDS (7.3 vs. 7.4, $p=0.95$) and sleep quality (6.5 vs. 6.1, $p=0.73$) were highly associated with depression and anxiety. In CD patients, motor severity did not explain variation in fatigue ($\Delta R^2=0.06$, $p=0.15$), EDS ($\Delta R^2=0.00$, $p=0.96$) and sleep quality ($\Delta R^2=0.04$, $p=0.38$) scores. Fatigue, EDS, psychiatric co-morbidity and pain predicted a decreased QoL.

Conclusion: Independently from psychiatric co-morbidity and motor severity, fatigue appeared a primary NMS. Sleep-related measures were highly associated with psychiatric co-morbidity, but not with motor severity. Only NMS predicted HR-QoL, which emphasize the importance of attention to NMS in CD patients.

INTRODUCTION

Cervical Dystonia (CD) is a hyperkinetic movement disorder characterized by sustained or intermittent contractions of the cervical musculature, leading to abnormal head postures. Although defined by its motor symptoms, growing evidence indicates that non-motor symptoms (NMS) are an important part of the phenotype of CD [1–3] and that they have a profound effect on health-related quality of life (HR-QoL) [3–5].

While psychiatric co-morbidity has been studied more extensively, only a few studies investigated the prevalence and severity of fatigue, excessive daytime sleepiness and sleep quality in CD patients. Fatigue, referring to an increased level of perceived fatigue [6], has been described in 50 percent of the CD patients [7,8]. Daytime sleepiness scale scores, as reviewed by Hertenstein et al., were usually within the normal range in CD patients, while sleep quality has been found reduced in several studies [3]. Until now, it is still unknown whether these symptoms may be a response to or related with psychiatric co-morbidity, or if these symptoms are a secondary phenomenon in response to motor symptoms. Interestingly, symptoms of excessive daytime sleepiness and the disturbed sleep quality did not improve after botulinum toxin therapy despite significant improvement of dystonia motor severity [9], which would suggest that these symptoms may be a primary phenomenon in dystonia.

Although these former studies have shown that fatigue and sleep disturbances are highly prevalent in CD patients, methodological limitations were noted. Either an appropriate control group or an objective CD motor score were lacking. Moreover, not all studies examined the influence of depression, anxiety, pain and severity of motor symptoms on fatigue, excessive daytime sleepiness and sleep quality scores. HR-QoL and the most important predictors of a reduced HR-QoL were often not systematically assessed.

In this study, we examined the prevalence and severity of fatigue, excessive daytime sleepiness and sleep quality in CD patients and compared this with matched controls. In addition, we calculated the fatigue and sleep-related scores corrected for depression and anxiety. Then, in the patient group, we used a stepwise linear regression model to examine whether motor characteristics could explain an additional part in the variation in fatigue and sleep-related measures, besides the known association with psychiatric co-morbidity and pain. In the last section, we assessed which motor- and/or NMS were the most important contributors to a decreased HR-QoL.

METHODS

Subjects

We included patients with a clinically diagnosed idiopathic CD and age and gender matched controls. An exclusion criterion for the patients was onset of CD before 18yr. Additional exclusion criteria for all subjects included other relevant neurological co-morbidity and the use of antidepressant medication. All subjects previously participated in a study about psychiatric co-morbidity, see also Smit et al [10]. Informed consent was obtained from all participants and the study was approved by the local ethics committee.

Fatigue, excessive daytime sleepiness, sleep quality and HRQoL

Fatigue was evaluated by the Fatigue Severity Scale (FSS). The FSS quantifies the impact of fatigue and contains 7 items which could be scored on a scale from one to nine. The summed score (max 63) is divided by nine and a total score of more than four is regarded as an indicator of fatigue [11]. Excessive daytime sleepiness was assessed by the self-administered Epworth Sleepiness Scale (ESS). A score of ten or higher (range 0-24) indicates excessive daytime sleepiness [12]. Quality of sleep was evaluated by the Pittsburgh Sleep Quality Index (PSQI). A score of five or higher (range 0-21) indicates impaired sleep quality [13]. The severity of depression and anxiety were measured with the Beck Depression Inventory (BDI) [14] and the Beck Anxiety Inventory (BAI) [15]. HR-QoL was assessed by the RAND-36 item Health Survey (RAND-36) [16]. For all scales, a score of zero indicates no complaints, and increasing scores indicates increasing severity.

Motor assessment

Motor assessment was performed by using a systematic video protocol. To obtain the least influenced motor score, 39 patients were videotaped two weeks prior to their next botulinum toxin (BoNT) injections and five patients were videotaped in the first week after BoNT injections. CD severity was scored with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [17]. Because the TWSTRS does not include severity of jerks and tremor, jerks and tremor were additionally scored by using the 7-point Clinical Global Impression Scale: CGI-S jerks-tremor [18]. The motor function was independently scored by two experts (MS, VH) and revealed good agreement (>0.80 Intraclass Correlation Coefficients, two-way mixed, absolute agreement, average measures). The average score of the two experts was used in the statistical analysis.

Statistical analysis

Statistical analysis was performed using PASW Statistics 22 (SPSS Statistics, USA) and differences were considered significant at $p<0.05$. Demographic and clinical data were compared between CD patients and controls using the Pearson $\chi 2$ test/Fisher's exact test or the Mann-Whitney U test. An Analysis of Covariance (ANCOVA) was performed to control for the potential confounding effect of depression and anxiety on the FSS, ESS

and PSQI. For this purpose, the BDI and BAI score were combined to one factor using factor analysis.

In the CD patient group, influence of motor severity on fatigue, excessive daytime sleepiness and sleep quality was assessed with a stepwise multiple linear regression analysis. In the first step, we assessed the influence of depression, anxiety and the severity of pain on the FSS, ESS and PSQI. In the second step, we assessed whether motor characteristics, including dystonia, jerks and tremor, could explain an additional part of the variation in FSS, ESS and PSQI scores.

The influence of clinical variables on HR-QoL in CD patients was first assessed with a univariate analysis. Because we had a relatively small number of patients, this was performed with the Spearman's rho test, or, for the discrete dichotomous variables, with the Pearson's *r* test. With multiple regression analysis, we then determined the influence of variables with a p-value of <0.05 in the univariate analysis on the HR-QoL domains using backward elimination. Assumptions of the linear regression and multicollinearity were checked.

RESULTS

Clinical characteristics

This study included 44 CD patients (mean 51yr, range 20-80) and 43 controls (mean 54yr, range 25-83) (Table 1). Nine CD patients used benzodiazepines, one patient trihexyphenidyl, one gabapentin and one pregabalin. In the control group, three subjects used benzodiazepines. Benzodiazepine type, dosage and frequency were highly variable. ESS scores in CD patients were significantly higher in those using psychoactive medication: 12.6 (±6.7) vs. 7.7 (±6.6), p=0.04, but no relation with sleep quality was found. (Suppl. table 1). None of the participants was officially diagnosed with restless legs syndrome. Snoring was significantly more prevalent in CD patients as compared to controls: 68.2% vs. 39.5%, p<0.01. Breath holding spells were also more prevalent in CD patients, although not significantly: 18.2% vs. 7.0%, p=0.12.

The CD patients had a mean dystonia duration of 13.3yrs (±11.2). The mean total TWSTRS score was 34.1 (±13.0) and the mean CGI-S jerks/tremor score was 2.5 (±1.3). Patients scored significantly worse on the FSS (4.4 (±1.7) vs. 2.7 (±1.4), p<0.01), on the ESS (8.8 (±6.9) vs. 5.8 (±4.9), p=0.04), and on the PSQI (7.4 (±3.9) vs. 5.1 (±4.4), p<0.01). Also on the depression rating scale (10.6 (±7.3) vs. 4.5 (±5.0), p<0.01) and the anxiety rating scale (9.3 (±6.8) vs. 4.0 (±4.2), p<0.01), patients scored significantly worse.

Based on the criteria as described in the method section, significantly more patients fulfilled the criteria of fatigue (28 (63.3%) vs. 7 (16.7%), p<0.01), excessive daytime

sleepiness (19 (43.2%) vs. 9 (20.9%), p=0.03) and impaired sleep quality (34 (77.3%) vs. 18 (41.9%), p<0.01) as compared to controls.

After controlling for depression and anxiety, patients still scored significantly worse on the FSS (mean 4.0 vs. 3.1 p=0.01). In contrast, the ESS (mean 7.3 vs. 7.4 p=0.95) and the PSQI (mean 6.5 vs. 6.1 p=0.73) were not significantly different between groups after controlling for depression and anxiety (Table 1).

Table 1
Clinical characteristics.

	CD (n=44)		**HC (n=43)**		**p-value**	
Age	54 (10.6)		54 (11.3)		0.93	
Gender M/F (n)	12/ 32		11/ 32		0.86	
Motor characteristics						
Duration of Dystonia	13.3 (11.2)					
TWSTRS Total - TWSTRS Severity - TWSTRS Disability - TWSTRS Pain	34.1 (13.0) 16.0 (4.6) 10.2 (5.5) 7.9 (6.2)					
CGI-S jerks/tremor	2.5 (1.3)					
Non-motor characteristics						
BDI	10.6 (7.3)		4.5 (5.0)		<0.01	
BAI	9.3 (6.8)		4.0 (4.2)		<0.01	
	Uncorrected	*Corrected*	*Uncorrected*	*Corrected*	*Uncorrected*	*Corrected*
FSS	4.4 (1.7)	4.0	2.7 (1.4)	3.1	<0.01	0.01
ESS	8.8 (6.9)	7.3	5.8 (4.9)	7.4	0.04	0.95
PSQI	7.4 (3.9)	6.5	5.1 (4.4)	6.1	<0.01	0.73

Values are presented as mean (SD) or n (as indicated). Corrected values are controlled for depression and anxiety as one factor by using ANCOVA. CD = cervical dystonia. HC = healthy control.

Supplementary table 1
The effect of psychoactive medication on FSS, ESS and PSQI scores.

	CD without medication (n=34)	CD with medication (n=10)	p-value	Control without medication (n=40)	Control with medication (n=3)	p-value
FSS	4.15 (1.72)	5.27 (1.59)	0.07	2.64 (1.39)	3.22 (1.13)	0.34
ESS	7.74 (6.58)	12.60 (6.71)	0.04	5.73 (5.04)	7.00 (3.61)	0.36
PSQI	6.97 (3.97)	9.00 (3.43)	0.10	4.78 (4.09)	10.00 (6.25)	0.10

Values are presented as mean (SD). CD = cervical dystonia.

Predictors of fatigue, excessive daytime sleepiness and sleep disturbances

To assess whether the FSS, ESS and PSQI scores in the CD patient group were associated with the severity of the dystonic posturing, jerks and/or tremor, we performed a stepwise linear regression analysis. In the first step, we assessed the influence of depression, anxiety and the severity of pain on the FSS, ESS and PSQI. In the second step, we assessed the influence of the severity of dystonia, jerks and tremor in addition to step one. Thus, in the first step we included factors that are known from the literature to have an effect on fatigue and sleep-related measures and in the second step we assessed whether motor characteristics could explain an additional part of the variation in fatigue and sleep-related measures.

The FSS was significantly influenced by depression, anxiety and pain (R^2=0.37 for step 1, p<0.01), with a significant influence of the depressive symptoms (β=0.44, p=0.01) (Table 2, suppl. table 2). Motor severity did not influence fatigue scores (ΔR^2=0.06 for step 2, p=0.15), although the CGI-S jerks/tremor score showed a mild association with the FSS (β=0.27, p=0.05).

The ESS was also significantly influenced by step 1 (R^2=0.31 for step 1, p<0.01), with depression being the only significant predictor (β=0.57, p<0.01). In step 2, severity of dystonia, jerks and tremor did not significantly influence the model (ΔR^2=0.00 for step 2, p=0.96).

The PSQI was significantly influenced by the TWSTRS pain score (β=0.40, p=0.01) (R^2=0.26 for step 1, p=0.01), while depressive symptoms had no significant influence. Motor symptoms did not influence the PSQI (ΔR^2=0.04 for step 2, p=0.38).

HR-QoL and predictors of a decreased HR-QoL

The patient group scored significantly worse on the first eight domains of the HR-QoL rating scale as compared to the healthy control group (Table 3).

Table 2
Influence of motor symptom severity on the FSS, ESS and PSQI.

	Step 1		Step 2	
	R^2	p-value	ΔR^2	p-value
FSS	0.37	<0.01	0.06	0.15
ESS	0.31	<0.01	0.00	0.96
PSQI	0.26	0.01	0.04	0.38

Multiple linear regression analysis to predict the effect of depression, anxiety and pain (step 1) on the FSS, ESS and PSQI, and the additional effect of severity of motor symptoms (step 2) in CD patients.

Supplementary table 2
Influence of motor symptom severity on the FSS, ESS and PSQI.

Domain	Predictors	B°	β	p-value
FSS	Step 1			
	- Constant	2.56 (0.45)		
	- BDI	0.11 (0.04)	0.44	0.01
	- BAI	0.03 (0.04)	0.11	0.51
	- TWSTRS pain	0.06 (0.04)	0.22	0.12
	Step 2			
	- Constant	1.82 (0.92)		
	- BDI	0.13 (0.04)	0.53	<0.01
	- BAI	0.00 (0.04)	0.00	0.99
	- TWSTRS pain	0.07 (0.04)	0.25	0.09
	- TWSTRS severity	-0.01 (0.05)	-0.03	0.82
	- CGI-S jerks/tremor	0.36 (0.18)	0.27	0.05
	R^2=0.37 for step 1 (p<0.01), ΔR^2=0.06 for step 2 (p=0.15)			
ESS	Step 1			
	- Constant	3.33 (1.83)		
	- BDI	0.53 (0.15)	0.57	<0.01
	- BAI	-0.02 (0.17)	-0.02	0.93
	- TWSTRS pain	0.01 (0.16)	0.01	0.95
	Step 2			
	- Constant	2.64 (3.94)		
	- BDI	0.52 (0.16)	0.56	<0.01
	- BAI	-0.00 (0.19)	-0.00	0.99
	- TWSTRS pain	-0.01 (0.17)	-0.01	0.97
	- TWSTRS severity	0.06 (0.21)	0.04	0.78
	- CGI-S jerks/tremor	-0.07 (0.76)	-0.01	0.93
	R^2=0.31 for step 1 (p<0.01), ΔR^2=0.00 for step 2 (p=0.96)			
PSQI	Step 1			
	- Constant	4.13 (1.09)		
	- BDI	0.16 (0.09)	0.30	0.08
	- BAI	-0.04 (0.10)	-0.07	0.70
	- TWSTRS pain	0.25 (0.09)	0.40	0.01
	Step 2			
	- Constant	1.86 (2.28)		
	- BDI	0.15 (0.09)	0.27	0.12
	- BAI	-0.01 (0.11)	-0.02	0.93
	- TWSTRS pain	0.21 (0.10)	0.33	0.04
	- TWSTRS severity	0.17 (0.12)	0.20	0.17
	- CGI-S jerks/tremor	-0.12 (0.44)	-0.04	0.79
	R^2=0.26 for step 1 (p=0.01), ΔR^2=0.04 for step 2 (p=0.38)			

Multiple linear regression analysis to predict the effect of depression, anxiety and pain (step 1) on the FSS, ESS and PSQI, and the additional effect of severity of motor symptoms (step 2). The constant indicates the b0, ie the Y intercept. B°=unstandardized coefficient with standard error in parenthesis. β=standardized regression coefficient.

The univariate analysis showed that a decreased HR-QoL in CD patients was associated with fatigue, excessive daytime sleepiness, sleep disturbances, depression, anxiety and pain, while motor symptoms were not associated with HR-QoL (Table 4).

The multiple linear regression analysis revealed that the FSS had a significant negative influence on the domain physical functioning (β=-0.60, p<0.01), on the domain mental health (β=-0.26, p=0.03) and on the domain pain (β=-0.37, p<0.01) (Table 5). The ESS had a significant negative influence on the domain mental health (β=-0.39, p<0.01) and on the domain vitality (β=-0.36, p=0.01). The PSQI was not associated with any of the HR-QoL domains. In addition to fatigue and excessive daytime sleepiness, the severity of depression, anxiety and pain was also negatively associated with the domains physical functioning, social functioning, role limitation emotional, vitality and pain. Motor symptoms were not included in the multiple regression analysis, because they were not associated with HR-QoL in the univariate analysis.

Table 3
HR-QoL in patients and healthy controls.

HRQoL domain	CD (n=44)	HC (n=43)	p-value
Physical functioning	75.0 (55.0 – 90.0)	95.0 (90.0 – 100.0)	<0.01
Social functioning	75.0 (62.5 – 88.0)	100.0 (88.0 – 100.0)	<0.01
Role limitation physical	50.0 (0.0 – 100.0)	100.0 (75.0 – 100.0)	<0.01
Role limitation emotional	100.0 (42.4 – 100.0)	100.0 (100.0 – 100.0)	
Mental health	72.0 (63.5 – 80.0)	88.0 (80.0 – 92.0)	<0.01
Vitality	55.0 (40.0 – 68.8)	80.0 (65.0 – 85.0)	<0.01
Pain	62.0 (45.0 – 79.9)	90.0 (67.0 – 100.0)	<0.01
General health perception	57.5 (41.3 – 70.0)	80.0 (70.0 – 90.0)	<0.01
Expected health change	50.0 (31.3 – 50.0)	50.0 (50.0 – 50.0)	0.13

Values are presented as median (interquartile ranges).

Table 4
Correlations between the domains of HR-QoL and clinical variables in CD patients.

	PF	SF	RLP	RLE	MH	V	P	GHP	EHC
Demographic characteristics									
Age	0.14	0.22	0.36*	0.19	0.29	0.38**	0.19	0.06	-0.05
Gender	-0.03	-0.19	-0.06	-0.11	-0.13	-0.03	-0.06	0.03	-0.13
Non-motor									
FSS	-0.71**	-0.54**	-0.55**	-0.37*	-0.37*	-0.57**	-0.52**	-0.46**	-0.15
ESS	-0.55**	-0.61**	-0.42**	-0.24	-0.54**	-0.57**	-0.28	-0.35*	-0.11
PSQI	-0.29	-0.33*	-0.33*	-0.14	-0.32*	-0.28	-0.35*	-0.36*	0.08
BDI	-0.51**	-0.62**	-0.41**	-0.61**	-0.69**	-0.65**	-0.44**	-0.44**	0.02
BAI	-0.43**	-0.16	-0.31*	-0.51**	-0.70**	-0.58**	-0.42**	-0.48**	-0.02
Dystonia rating scales									
Dystonia duration	-0.09	0.03	-0.04	-0.20	0.04	0.07	0.11	0.06	-0.32*
TWSTRS Severity	-0.13	0.17	0.11	0.12	0.08	0.08	-0.10	-0.08	-0.01
TWSTRS Pain	-0.44**	-0.20	-0.41**	-0.38*	-0.24	-0.37*	-0.61**	-0.36*	-0.13
CGI-S jerks/tremor	0.01	0.21	0.06	0.19	0.10	0.04	-0.02	0.17	-0.08

Data are 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

Table 5
Predictors of a decreased HR-QoL in CD patients.

Domain	Predictor(s)	Adjusted R^2	B°	β	p-value
Physical functioning	FSS	0.48	-0.82 (0.16)	-0.60	<0.01
	TWSTRS pain		-0.82 (0.40)	-0.24	0.05
Social functioning	BDI	0.37	-1.88 (0.37)	-0.62	<0.01
Role limitation physical	-				
Role limitation emotional	BDI	0.48	-2.80 (0.61)	-0.52	<0.01
	TWSTRS pain		-2.50 (0.72)	-0.39	<0.01
Mental health	BDI	0.67	-0.84 (0.24)	-0.44	<0.01
	ESS		-0.81 (0.24)	-0.39	<0.01
	BAI		-0.79 (0.23)	-0.38	<0.01
	FSS		-0.24 (0.11)	-0.26	0.03
Vitality	BDI	0.49	-1.03 (0.30)	-0.45	<0.01
	ESS		-0.89 (0.32)	-0.36	0.01
Pain	TWSTRS pain	0.45	-1.76 (0.46)	-0.47	<0.01
	FSS		-0.56 (0.18)	-0.37	<0.01
General health perception	-				
Expected health change	-				

Clinical characteristics significantly associated with a decreased HR-QoL, assessed with multiple lineair regression analysis after backward elimination. For the variables with a signifincant influence, we calculated the adjusted R2, the B° (unstandardized coefficient with standard error in parenthesis) and β (standardized regression coefficient).

DISCUSSION

This study shows a significantly increased prevalence of fatigue, excessive daytime sleepiness and an impaired sleep quality in CD patients as compared to the controls. The level of perceived fatigue in CD patients appeared to be increased independently from psychiatric co-morbidity and motor symptom severity. Excessive daytime sleepiness and sleep quality were highly associated with depression and anxiety, but not with motor symptoms severity.

Compared to other studies, we found a higher prevalence of fatigue in CD patients. In our cohort, 63.3% fulfilled the criteria of fatigue, while two other studies found a prevalence of 50% [7,8]. One explanation could be that depressive symptom scores were also higher in our cohort compared to the study of Wagle Shukla et al. (10.6 vs. 6.8) [7]. As depression is positively associated with fatigue scores, this might explain the higher frequency of fatigue in our patient group. However, after correction for depression and anxiety, fatigue scores were still significantly increased in our CD patients. Moreover, we also found higher excessive daytime sleepiness scores (8.8 vs. 7.4), a variable which is also positively associated with fatigue. Severity of motor symptoms did not significantly influence fatigue scores, although severity of jerks/tremor showed a mild association with the perceived level of fatigue. Similar to other neurological disorders like Parkinson's disease (PD) and multiple sclerosis in which fatigue is a primary non-motor symptom [6], fatigue might be part of the phenotype of dystonia instead of a secondary phenomenon. Dysfunction of the basal ganglia is likely to form a shared underlying mechanism of both the dystonia motor pathophysiology and fatigue [6,19]. Especially serotonergic functioning in the basal ganglia might contribute to both fatigue and dystonia [20]. In PD, decreased serotonin transporter binding was found in PD patients, which was even lower in PD patients with fatigue [21]. These findings reinforce the hypothesis of a primary mechanism, intrinsic to dystonia, being responsible for the perception of fatigue in CD patients.

Severity of excessive daytime sleepiness and impaired sleep quality was similar to the scores found in other studies [3], and even more related to depressive and anxiety symptoms. Pain, present in 77.3% of our patients, also appeared to be significantly associated with an impaired sleep quality, and excessive daytime sleepiness was related with medication use. The severity of dystonia and/or jerks/tremor was not associated with excessive daytime sleepiness or an impaired sleep quality. A different approach to assess the influence of motor symptoms was used by Eichenseer et al, who examined patients before and after botulinum toxin (BoNT) treatment. While BoNT significantly improved the motor symptoms, there was no effect on the excessive daytime sleepiness and sleep quality scores [9]. Both approaches suggest that the severity of motor symptoms does not significantly contribute to excessive daytime sleepiness or an impaired sleep quality. Besides the influence of depression and pain, other factors such as restless legs syndrome (RLS) could possibly also contribute. As described by Paus et al., the

prevalence of RLS in CD was increased and associated with an impaired sleep quality [22]. None of our participants had a medical history of RLS, but it was not systematically investigated in our study. Medication like benzodiazepines or GABAergic agents was also related to higher excessive daytime sleepiness scores in our patient cohort, but not to impaired sleep quality. Due to the use of several types of medication, with different doses and variable frequencies, raising from sporadically to daily use, it was not possible to perform a reliable correction for medication use. However, the study of Eichenseer et al. did not found an influence of benzodiazepine use on sleep impairment in CD patients [9], which suggests that medication does not play a major role in altered sleep in CD patients. HR-QoL in CD patients is not only influenced by psychiatric co-morbidity [5], but fatigue and excessive daytime sleepiness also appeared to be significant contributors to a decreased HR-QoL. The influence of tiredness on HR-QoL has previously been described by Soeder et al., although they did not use a CD specific motor scale and could therefore not exclude the influence of motor symptoms [4]. In our study, the severity of dystonia and the severity of jerks and tremor were not associated with a decreased HR-QoL. The influence of fatigue and excessive daytime sleepiness on HR-QoL highlights the need for systematic screening of these symptoms in the daily practice, and to treat possible contributing factors like depression and pain.

This study had several limitations. First, our results could have been biased by the use of medication. Nine patients and two healthy controls used benzodiazepines, which could have induced sedative effects and a reduced sleep quality [3]. On the other hand, the exclusion of patients using anti-depressant medication could also have caused a selection bias by excluding subjects with high depressive scores. In total, we did not include eight patients using various antidepressants, and within the different hospitals several additional patients were not asked to participate because of known medication use. As depression appeared to be highly correlated with fatigue and excessive daytime sleepiness, this could have influenced our results. Therefore, increased fatigue, excessive daytime sleepiness and sleep disturbances scores in our cohort are possibly an underestimation, which emphasizes the need to screen for these symptoms in the daily practice. Second, with our study we only focused on the subjective sensation of fatigue, excessive daytime sleepiness and sleep quality. In future studies, objective measures to study fatigability or sleep quality, like electromyography or polysomnography, would be of help to understand the underlying pathophysiological mechanisms.

In conclusion, high rates of fatigue, excessive daytime sleepiness and sleep disturbances were detected in our study in CD patients. Independently from psychiatric co-morbidity, pain and motor severity, fatigue appeared to be a primary NMS. Sleep-related measures were highly associated with depression, anxiety and pain, but not with motor symptom severity. Importantly, only NMS significantly influenced HR-QoL, while severity of motor symptoms had no influence on any of the HR-QoL domains. Our results suggest that fatigue, excessive daytime sleepiness and a decreased sleep quality are correlated

with psychiatric comorbidity but must be seen independently from motor symptoms and require different treatment approaches. Future studies are warranted to investigate pathophysiological mechanisms behind fatigue and impaired sleep quality in dystonia patients and to assess if targeted treatment of fatigue, excessive daytime sleepiness and sleep disturbances could improve HR-QoL in CD patients.

REFERENCES

[1] M. Stamelou, M.J. Edwards, M. Hallett, K.P. Bhatia, The non-motor syndrome of primary dystonia: clinical and pathophysiological implications, Brain. 135 (2012) 1668–1681. doi:10.1093/brain/awr224 [doi].

[2] M. Zurowski, W.M. McDonald, S. Fox, L. Marsh, Psychiatric comorbidities in dystonia: emerging concepts, Mov. Disord. 28 (2013) 914–920. doi:10.1002/mds.25501 [doi].

[3] E. Hertenstein, N.K. Tang, C.J. Bernstein, C. Nissen, M.R. Underwood, H.K. Sandhu, Sleep in patients with primary dystonia: A systematic review on the state of research and perspectives, Sleep Med. Rev. (2015). doi:S1087-0792(15)00070-2 [pii].

[4] A. Soeder, B.M. Kluger, M.S. Okun, C.W. Garvan, T. Soeder, C.E. Jacobson, et al., Mood and energy determinants of quality of life in dystonia, J. Neurol. 256 (2009) 996–1001. doi:10.1007/s00415-009-5060-3 [doi].

[5] Y. Ben-Shlomo, L. Camfield, T. Warner, E. collaborative group, What are the determinants of quality of life in people with cervical dystonia?, J. Neurol. Neurosurg. Psychiatry. 72 (2002) 608–614.

[6] B.M. Kluger, L.B. Krupp, R.M. Enoka, Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy, Neurology. 80 (2013) 409–416. doi:10.1212/WNL.0b013e31827f07be [doi].

[7] A. Wagle Shukla, R. Brown, K. Heese, J. Jones, R.L. Rodriguez, I.M. Malaty, et al., High rates of fatigue and sleep disturbances in dystonia, Int. J. Neurosci. (2015) 1–8. doi:10.3109/00207454.2015.1085035 [doi].

[8] L. Klingelhoefer, D. Martino, P. Martinez-Martin, A. Sauerbier, A. Rizos, W. Jost, et al., Non-motor symptoms and focal cervical dystonia: observations from 102 patients, 4(3-4):117-120. (2014). doi:10.1016/j.baga.2014.10.002.

[9] S.R. Eichenseer, G.T. Stebbins, C.L. Comella, Beyond a motor disorder: a prospective evaluation of sleep quality in cervical dystonia, Parkinsonism Relat. Disord. 20 (2014) 405–408. doi:10.1016/j.parkreldis.2014.01.004 [doi].

[10] M. Smit, A. Kuiper, V. Han, V.C. Jiawan, G. Douma, B. van Harten, et al., Psychiatric co-morbidity is highly prevalent in idiopathic cervical dystonia and significantly influences health-related quality of life: Results of a controlled study, Parkinsonism Relat. Disord. (2016). doi:S1353-8020(16)30216-4 [pii].

[11] L.B. Krupp, N.G. LaRocca, J. Muir-Nash, A.D. Steinberg, The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus, Arch. Neurol. 46 (1989) 1121–1123.

[12] M.W. Johns, A new method for measuring daytime sleepiness: the Epworth sleepiness scale, Sleep. 14 (1991) 540–545.

[13] D.J. Buysse, C.F. Reynolds 3rd, T.H. Monk, S.R. Berman, D.J. Kupfer, The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research, Psychiatry Res. 28 (1989) 193–213. doi:0165-1781(89)90047-4 [pii].

[14] A.T. BECK, A systematic investigation of depression, Compr. Psychiatry. 2 (1961) 163–170.

[15] A.T. Beck, N. Epstein, G. Brown, R.A. Steer, An inventory for measuring clinical anxiety: psychometric properties, J. Consult. Clin. Psychol. 56 (1988) 893–897.

[16] K.I. van der Zee, R. Sanderman, Het meten van de algemene gezondheidstoestand met de RAND-36, een handleiding. Groningen: Rijksuniversiteit Groningen, Noordelijk Centrum voor Gezondheidsvraagstukken., (1992).

[17] E.S. Consky, A.E. Lang, Clinical assessments of patients with cervical dystonia. In: Jankovic J, Hallett M, editors. Therapy with botulinum toxin. New York, NY: Marcel Dekker, (1994) 211–237.

[18] W. Guy, The Clinical Global Impression scale. In: ECDEU Assessment Manual for Psychopharmacology-Revised. Rockville, MD: US Dept. of Health, Education and Welfare, ADAMHA, NIMH Psychopharmacology Research Branch, (1976) 218. doi:222.

[19] M. Vidailhet, D. Grabli, E. Roze, Pathophysiology of dystonia, Curr. Opin. Neurol. 22 (2009) 406–413. doi:10.1097/WCO.0b013e32832d9ef3 [doi].

[20] M. Smit, A.L. Bartels, M. van Faassen, A. Kuiper, K.E. Niezen-Koning, I.P. Kema, et al., Serotonergic perturbations in dystonia disorders-a systematic review, Neurosci. Biobehav. Rev. 65 (2016) 264–275. doi:S0149-7634(15)30152-4 [pii].

[21] N. Pavese, V. Metta, S.K. Bose, K.R. Chaudhuri, D.J. Brooks, Fatigue in

Parkinson's disease is linked to striatal and limbic serotonergic dysfunction, Brain. 133 (2010) 3434–3443. doi:10.1093/brain/awq268 [doi].

[22] S. Paus, J. Gross, M. Moll-Muller, F. Hentschel, A. Spottke, B. Wabbels, et al., Impaired sleep quality and restless legs syndrome in idiopathic focal dystonia: a controlled study, J. Neurol. 258 (2011) 1835–1840. doi:10.1007/s00415-011-6029-6 [doi].