Fatigue, Sleep Disturbances, and Their influence on Quality of Life In Cervical Dystonia Patients

Smit, Marenka; Kamphuis, A; Bartels, Anna L.; Han, Vladimir; Stewart, Roy E.; Zijdewind, Clasina; de Koning-Tijssen, Marina. A. J.

Published in:
Movement Disorders Clinical Practice

DOI:
10.1002/mdc3.12459

Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Fatigue, Sleep Disturbances, and Their Influence on Quality of Life in Cervical Dystonia Patients

Marenka Smit, MD,[1] Arwen S. J. Kamphuis, BSc,[1] Anna L. Bartels, MD, PhD,[1,2] Vladimir Han, MD,[3,4] Roy E. Stewart, PhD,[5] Inge Zijdewind, PhD,[6] Marina A. Tijssen, MD, PhD[1,]*

Abstract: **Background:** Nonmotor symptoms (NMS) are highly prevalent in cervical dystonia (CD). In general, fatigue and sleep are important NMS that determine a decreased health-related quality of life (HR-QoL), but their influence in CD is unknown. The authors systematically investigated fatigue, excessive daytime sleepiness (EDS), and sleep quality in patients with CD and controls and assessed the influence of psychiatric comorbidity, pain, and dystonia motor severity. They also examined the predictors of HR-QoL. **Methods:** The study included 44 patients with CD and 43 matched controls. Fatigue, EDS, and sleep quality were assessed with quantitative questionnaires and corrected for depression and anxiety using analysis of covariance. The Toronto Western Spasmodic Torticollis Rating Scale and the Clinical Global Impression Scale-jerks/tremor subscale were used to score motor severity and to assess 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, and predictors of HR-QoL were assessed using multiple regression. **Results:** Fatigue scores were increased independently from psychiatric comorbidity (4.0 vs. 2.7; $P < 0.01$), whereas 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 patients with CD, motor severity did not explain the variations in fatigue (change in the correlation coefficient [ΔR^2] = 0.06; $P = 0.15$), EDS ($\Delta R^2 = 0.00$; $P = 0.96$), or sleep quality ($\Delta R^2 = 0.04$; $P = 0.38$) scores. Fatigue, EDS, psychiatric comorbidity, and pain predicted a decreased QoL. **Conclusion:** Independent from psychiatric comorbidity and motor severity, fatigue appeared to be a primary NMS. Sleep-related measures were highly associated with psychiatric comorbidity, but not with motor severity. Only NMS predicted HR-QoL, which emphasizes the importance of attention to NMS in patients with CD.

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 CD is by its motor symptoms, growing evidence indicates that nonmotor 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]

Although psychiatric comorbidity has been studied more extensively, only a few studies have investigated the prevalence and severity of fatigue, excessive daytime sleepiness, and sleep quality in patients with CD. Fatigue, which refers to an increased level of perceived fatigue,[6] has been described in 50%

[1]Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [2]Department of Neurology, Ommelander Hospital Group, Delfzijl, the Netherlands; [3]Department of Neurology, Safarik University, Kosice, Slovakia; [4]Department of Neurology, University Hospital L. Pasteur, Kosice, Slovakia; [5]Department of Health Sciences, Community and Occupational Medicine, University Medical Center Groningen, Groningen, the Netherlands; [6]Department of Neuroscience, University Medical Center Groningen, Groningen, the Netherlands

***Correspondence to:** Dr. Marina A. Tijssen, Department of Neurology, University Medical Center Groningen, Hanzeplein 1, 9700RB Groningen, the Netherlands; E-mail: m.a.j.de.koning-tijssen@umcg.nl
Keywords: cervical dystonia, excessive daytime sleepiness, fatigue, health-related quality of life, sleep quality.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Supporting information may be found in the online version of this article.
Received 13 July 2016; revised 13 September 2016; accepted 26 October 2016.
Published online 5 December 2016 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12459

doi:10.1002/mdc3.12459

of patients with CD.[7,8] Daytime sleepiness scale scores, as reviewed by Hertenstein et al., are usually within the normal range in patients with CD, whereas sleep quality reportedly was reduced in several studies.[3] To date, it is still unknown whether these symptoms may be a response to or related with psychiatric comorbidity or whether they are a secondary phenomenon in response to motor symptoms. Interestingly, symptoms of excessive daytime sleepiness and disturbed sleep quality did not improve after botulinum toxin (BoNT) therapy a despite significant improvement of dystonia motor severity,[9] suggesting that these symptoms may be a primary phenomenon in dystonia.

Although the former studies have shown that fatigue and sleep disturbances are highly prevalent in patients with CD, 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 the current study, we examined the prevalence and severity of fatigue, excessive daytime sleepiness, and sleep quality in patients who had CD compared with a group of 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 other than the known association with psychiatric comorbidity and pain. In addition, we assessed which motor symptoms and/or NMS were the most important contributors to a decreased HR-QoL.

Patients and Methods

Participants

We included patients who had clinically diagnosed, idiopathic CD with a group of age-matched and sex-matched controls. An exclusion criterion for the patients was the onset of CD before age 18 years. Additional exclusion criteria for all participants included other relevant neurological comorbidity and the use of antidepressant medication. All participants had previously been included in a study about psychiatric comorbidity (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 HR-QoL

Fatigue was evaluated using the Fatigue Severity Scale (FSS). The FSS quantifies the impact of fatigue and contains 7 items, which are scored on a scale from 1 to 9. The summed score (maximum, 63) is divided by 9, and a total score of more than 4 is regarded as an indicator of fatigue.[11] Excessive daytime sleepiness was assessed using the self-administered Epworth Sleepiness Scale (ESS), in which a score of 10 or higher (range, 0–24) indicates excessive daytime sleepiness.[12] Quality of sleep was evaluated using the Pittsburgh Sleep Quality Index (PSQI), in which a score of 5 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] respectively. HR-QoL was assessed using RAND-36 item Health Survey (RAND-36).[16] For all scales, a score of zero indicates no complaints, and increasing scores indicate 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 2 weeks before their next BoNT injections, and 5 patients were videotaped in the first week after BoNT injections. CD severity was scored using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).[17] Because the TWSTRS does not include severity of jerks and tremor, jerks and tremor also were scored using the 7-point Clinical Global Impression Scale: CGI-S jerks-tremor.[18] Motor function was independently scored by 2 experts (M.S. and V.H.) and revealed good agreement (>0.80 intraclass correlation coefficients, 2-way mixed, absolute agreement, average measures). The average score of the 2 experts was used in the statistical analysis.

Statistical Analysis

Statistical analyses were performed using the PASW Statistics 22 software package (SPSS Statistics; IBM Corporation, Armonk, NY), and differences were considered significant at $P < 0.05$. Demographic and clinical data were compared between patients with CD and controls using the Pearson $\chi 2$ test/Fisher 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 scores were combined into 1 factor using factor analysis.

In the group of patients with CD, the 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 patients with CD was first assessed in a univariate analysis. Because we had a relatively small number of patients, this was performed with the Spearman's ρ test, or, for the discrete dichotomous variables, with the Pearson r test. In multiple regression analysis, we then determined the influence of variables that had P values <0.05 in the univariate analysis on the HR-QoL domains using

doi:10.1002/mdc3.12459

backward elimination. Assumptions of the linear regression and multicollinearity were checked.

Results

Clinical Characteristics

This study included 44 patients with CD (mean age, 51 years; range, 20–80 years) and 43 controls (mean age, 54 years; range, 25–83 years) (Table 1). Nine patients with CD used benzodiazepines, 1 used trihexyphenidyl, 1 used gabapentin, and 1 used pregabalin. In the control group, 3 participants used benzodiazepines. Benzodiazepine type, dosage, and frequency were highly variable. Mean ESS scores (±standard deviation) in patients with CD were significantly higher in those who were using psychoactive medication (mean ± standard deviation, 12.6 ± 6.7 vs. 7.7 ± 6.6; $P = 0.04$), but no relation with sleep quality was observed (Table S1). None of the participants were officially diagnosed with restless legs syndrome (RLS). Snoring was significantly more prevalent in patients with CD versus controls (68.2% vs. 39.5%; $P < 0.01$). Breath-holding spells also were more prevalent in CD patients, although the difference was not significant (18.2% vs. 7.0%, respectively; $P = 0.12$).

Patients with CD had a mean ± standard deviation dystonia duration of 13.3 ± 11.2 years. The mean ± standard deviation 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 than controls on the FSS (4.4 ± 1.7 vs. 2.7 ± 1.4; $P < 0.01$), the ESS (8.8 ± 6.9 vs. 5.8 ± 4.9; $P = 0.04$), and the PSQI (7.4 ± 3.9 vs. 5.1 ± 4.4; $P < 0.01$). In addition, patients scored significantly worse 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; $P < 0.01$).

Based on the criteria described above (see Patients and Methods), significantly more patients fulfilled the criteria for fatigue (n = 28 [63.3%] vs. 7 [16.7%]; $P < 0.01$), excessive daytime sleepiness (n = 19 [43.2%] vs. 9 [20.9%]; $P = 0.03$) and impaired sleep quality (n = 34 [77.3%] vs. 18 [41.9%]; $P < 0.01$) compared with controls.

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

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 FSS, ESS, and PSQI scores. In the second step, we assessed the influence of the severity of dystonia, jerks, and tremor in addition to Step 1. 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 (correlation coefficient [R^2] = 0.37 for Step 1; $P < 0.01$), with a significant influence from depressive symptoms ($\beta = 0.44$; $P = 0.01$) (Table 2, S2). Motor severity did not influence fatigue scores (change in the correlation

TABLE 1 Clinical Characteristics

Characteristic	Mean ± SD		*P* value
	CD, n = 44	HC, n = 43	
Age, y	54 ± 10.6	54 ± 11.3	0.93
Sex: No. of men/women	12/32	11/32	0.86
Motor characteristics			
Duration of dystonia, years	13.3 ± 11.2		
TWSTRS score			
Total	34.1 ± 13.0		
Severity	16.0 ± 4.6		
Disability	10.2 ± 5.5		
Pain	7.9 ± 6.2		
CGI-S jerks/tremor	2.5 ± 1.3		
Nonmotor characteristics			
BDI score	10.6 ± 7.3	4.5 ± 5.0	<0.01
BAI score	9.3 ± 6.8	4.0 ± 4.2	<0.01
Uncorrected/corrected scores: Mean ± SD/mean[a]			
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

CD, cervical dystonia; HC, health controls; SD, standard deviation; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; CGI-S, Clinical Global Impression Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; FSS, Fatigue Severity Scale; ESS, Epsworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index.
[a]Corrected values are controlled for depression and anxiety as 1 factor by using analysis of covariance.

doi:10.1002/mdc3.12459

TABLE 2 Influence of Motor Symptom Severity on the Fatigue Severity Scale, the Epsworth Sleepiness Scale, and the Pittsburgh Sleep Quality Index*

	Step 1		Step 2	
Measure	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

ΔR^2, change in the correlation coefficient; FSS, Fatigue Severity Scale; ESS, Epsworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; R^2, correlation coefficient.
*Multiple linear regression analysis was used 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 patients with cervical dystonia.

coefficient [ΔR^2] = 0.06 for Step 2; $P = 0.15$), although the CGI-S jerks/tremor score showed a mild association with the FSS ($\beta = 0.27$; $P = 0.05$).

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 ($\beta = 0.57$; $P < 0.01$). In Step 2, severity of dystonia, jerks, and tremor did not significantly influence the model ($\Delta R^2 = 0.00$ for Step 2; $P = 0.96$).

The PSQI was significantly influenced by the TWSTRS pain score ($\beta = 0.40$; $P = 0.01$; $R^2 = 0.26$ for Step 1; $P = 0.01$), whereas depressive symptoms had no significant influence. Motor symptoms did not influence the PSQI score ($\Delta R^2 = 0.04$ for Step 2; $P = 0.38$).

HR-QoL and Predictors of a Decreased HR-QoL

The patient group scored significantly worse on the first 8 domains of the HR-QoL rating scale compared with the healthy control group (Table 3). Univariate analysis showed that decreased HR-QoL in patients with CD was associated with fatigue, excessive daytime sleepiness, sleep disturbances, depression, anxiety, and pain, whereas motor symptoms were not associated with HR-QoL (Table 4).

Multiple linear regression analysis revealed that the FSS had a significant negative influence on the domains physical functioning ($\beta = -0.60$; $P < 0.01$), mental health ($\beta = -0.26$;

TABLE 3 Health-related Quality of Life in Patients with Cervical Dystonia and Healthy Controls

	Median (Interquartile Range)		*P* value
HR-QoL Domain	CD, n = 44	HC, n = 43	
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

HR-QoL, health-related quality of life; CD, cervical dystonia; HC, healthy controls.

TABLE 4 Correlations between the Domains of Health-related Quality of Life and Clinical Variables in Patients with Cervical Dystonia

	Correlation Coefficient								
Variable	PF	SF	RLP	RLE	MH	Vitality	Pain	GHP	EHC
Demographic characteristics									
Age	0.14	0.22	0.36[a]	0.19	0.29	0.38[b]	0.19	0.06	−0.05
Sex	−0.03	−0.19	−0.06	−0.11	−0.13	−0.03	−0.06	0.03	−0.13
Nonmotor scores									
FSS	−0.71[b]	−0.54[b]	−0.55[b]	−0.37[a]	−0.37[a]	−0.57[b]	−0.52[b]	−0.46[b]	−0.15
ESS	−0.55[b]	−0.61[b]	−0.42[b]	−0.24	−0.54[b]	−0.57[b]	−0.28	−0.35[a]	−0.11
PSQI	−0.29	−0.33[a]	−0.33[a]	−0.14	−0.32[a]	−0.28	−0.35[a]	−0.36[a]	0.08
BDI	−0.51[b]	−0.62[b]	−0.41[b]	−0.61[b]	−0.69[b]	−0.65[b]	−0.44[b]	−0.44[b]	0.02
BAI	−0.43[b]	−0.16	−0.31[a]	−0.51[b]	−0.70[b]	−0.58[b]	−0.42[b]	−0.48[b]	−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[a]
TWSTRS severity	−0.13	0.17	0.11	0.12	0.08	0.08	−0.10	−0.08	−0.01
TWSTRS pain	−0.44[b]	−0.20	−0.41[b]	−0.38[a]	−0.24	−0.37[a]	−0.61[b]	−0.36[a]	−0.13
CGI−S jerks/tremor	0.01	0.21	0.06	0.19	0.10	0.04	−0.02	0.17	−0.08

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; FSS, Fatigue Severity Scale; ESS, Epsworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; CGI-S, Clinical Global Impression Scale.
[a]$P < 0.05$; [b]$P < 0.01$.

doi:10.1002/mdc3.12459

TABLE 5 Predictors of Decreased Health-related Quality of Life in Patients with Cervical Dystonia*

Domain	Predictor(s)	Adjusted R^2	B° (SE)	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	—				

R^2, correlation coefficient; B°, unstandardized coefficient; SE, standard error; β, standardized regression coefficient; FSS, Fatigue Severity Scale; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; BDI, Beck Depression Inventory; ESS, Epsworth Sleepiness Scale; BAI, Beck Anxiety Inventory.
*Clinical characteristics that were significantly associated with decreased health-related quality of life were assessed with multiple linear regression analysis after backward elimination. For variables that had a significant influence, the adjusted R^2, B° (with SE in parenthesis), and β were calculated.

$P = 0.03$) and pain ($\beta = -0.37$; $P < 0.01$) (Table 5). The ESS had a significant negative influence on the domains mental health ($\beta = -0.39$; $P < 0.01$) and vitality ($\beta = -0.36$; $P = 0.01$). 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.

Discussion

These results demonstrate a significantly increased prevalence of fatigue, excessive daytime sleepiness, and impaired sleep quality in patients who have CD compared with controls. The level of perceived fatigue in patients with CD appeared to be increase independent of psychiatric comorbidity and motor symptom severity. Excessive daytime sleepiness and sleep quality were highly associated with depression and anxiety, but not with motor symptoms severity.

Compared with other studies, we observed a higher prevalence of fatigue in patients with CD. In our cohort, 63.3% fulfilled the criteria of fatigue, whereas 2 other studies reported a prevalence of 50%.[7,8] One explanation could be that depressive symptom scores were also higher in our cohort compared with those in the study by Wagle Shukla et al. (10.6 vs. 6.8).[7] Because 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 population. Moreover, we also observed higher excessive daytime sleepiness scores (8.8 vs. 7.4), a variable that 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 NMS,[6] fatigue may 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] In particular, serotonergic functioning in the basal ganglia might especially contribute to both fatigue and dystonia.[20] Decreased serotonin transporter binding was observed in patients with PD, and was even lower in those who had PD with fatigue.[21] These findings reinforce the hypothesis that a primary mechanism, intrinsic to dystonia, may be responsible for the perception of fatigue in patients with CD.

The severity of excessive daytime sleepiness and impaired sleep quality was similar to the scores reported in other studies[3] and was related even more to depressive and anxiety symptoms. Pain, which was present in 77.3% of our patients, also appeared to be significantly associated with impaired sleep quality, and excessive daytime sleepiness was related to 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 assessing the influence of motor symptoms was used by Eichenseer et al., who examined patients before and after BoNT treatment. Although BoNT significantly improved the motor symptoms, there was no effect on the excessive daytime sleepiness or 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. Along with the influence of depression and pain, other factors, such as RLS, possibly also may contribute. As described by Paus et al., the prevalence of RLS in

doi:10.1002/mdc3.12459

CD was increased and was 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. Medications like benzodiazepines or GABAergic agents also were 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 and ranging from sporadic to daily use, it was not possible to perform a reliable correction for medication use. However, the study by Eichenseer et al. did not identify an influence of benzodiazepine use on sleep impairment in patients with CD,[9] suggesting that medication does not play a major role in altered sleep in CD.

HR-QoL in patients with CD not only is influenced by psychiatric comorbidity,[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 was previously described by Soeder et al., although they did not use a CD-specific motor scale and thus could not exclude the influence of motor symptoms.[4] In our study, the severity of dystonia and of jerks and tremor was not associated with decreased HR-QoL. The influence of fatigue and excessive daytime sleepiness on HR-QoL highlights the need for systematic screening of these symptoms in daily practice and the necessity of treating 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 2 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 antidepressant medication also could have caused a selection bias by excluding those with high depressive scores. In total, we did not include 8 patients who were using various antidepressants; and within the different hospitals, several additional patients were not asked to participate because of known medication use. Because depression appeared to be highly correlated with fatigue and excessive daytime sleepiness, this could have influenced our results. Therefore, the increased fatigue, excessive daytime sleepiness, and sleep disturbance scores in our cohort may be underestimated, emphasizing the need to screen for these symptoms in daily practice. Second, in our study, we focused only on the subjective sensations 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 helpful in understanding the underlying pathophysiological mechanisms.

In conclusion, high rates of fatigue, excessive daytime sleepiness, and sleep disturbances were detected in our study among patients with DC. Independent from psychiatric comorbidity, 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, whereas 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 patients with dystonia and to assess whether targeted treatment of fatigue, excessive daytime sleepiness, and sleep disturbances could improve HR-QoL in patients with CD.

Author Roles: 1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

M.S.: 1A, 1B, 1C, 2A, 2B, 3A
A.S.J.K.: 1C, 3A
A.L.B.: 1A, 1B, 2C, 3B
V.H.: 1A, 3B
R.E.S.: 2A, 3B
I.Z.: 1A, 3B
M.A.T: 1A, 1B, 3B

Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflict of Interest: The authors report no sources of funding and no conflicts of interest.

Financial Disclosures for the previous 12 months: Marenka Smit has received grants from the University Medical Center Groningen and Stichting Wetenschapsfonds Dystonie Vereniging. Vladimir Han has received grants from the Slovak Research and Development Agency and the Slovak Scientific Grant Agency as well as honoraria from Abbvie. Marina A. Tijssen has received research grants from Stichting Wetenschapsfonds Dystonie Vereniging, Prinses Beatrix Foundation, and Fonds NutsOhra and unrestricted grants for DystonieNet from Ipsen Pharmaceuticals, Allergan Pharmaceuticals, Medtronic. and Actelion. The remaining authors report no sources of funding and no conflicts of interest.

References

1. Stamelou M, Edwards MJ, Hallett M, Bhatia KP. The non-motor syndrome of primary dystonia: clinical and pathophysiological implications. *Brain* 2012;135:1668–1681.
2. Zurowski M, McDonald WM, Fox S, Marsh L. Psychiatric comorbidities in dystonia: emerging concepts. *Mov Disord* 2013;28:914–920.
3. Hertenstein E, Tang NK, Bernstein CJ, Nissen C, Underwood MR, Sandhu HK. Sleep in patients with primary dystonia: a systematic review on the state of research and perspectives. *Sleep Med Rev* 2016;26:95–107.
4. Soeder A, Kluger BM, Okun MS, et al. Mood and energy determinants of quality of life in dystonia. *J Neurol* 2009;256:996–1001.
5. Ben-Shlomo Y, Camfield L, Warner T; ESDE Collaborative Group. What are the determinants of quality of life in people with cervical dystonia? *J Neurol Neurosurg Psychiatry* 2002;72:608–614.
6. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology* 2013;80:409–416.

doi:10.1002/mdc3.12459

7. Wagle Shukla A, Brown R, Heese K, et al. High rates of fatigue and sleep disturbances in dystonia. *Int J Neurosci* 2015;126:928–935.

8. Klingelhoefer L, Martino D, Martinez-Martin P, et al. Nonmotor symptoms and focal cervical dystonia: observations from 102 patients. *Basal Ganglia* 2014;4:117–120.

9. Eichenseer SR, Stebbins GT, Comella CL. Beyond a motor disorder: a prospective evaluation of sleep quality in cervical dystonia. *Parkinsonism Relat Disord* 2014;20:405–408.

10. Smit M, Kuiper A, Han V, 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;30:7–12.

11. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46:1121–1123.

12. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540–545.

13. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.

14. Beck AT. A systematic investigation of depression. *Compr Psychiatry* 1961;2:163–170.

15. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988;56:893–897.

16. VanderZee KI, Sanderman R, Heyink JW, de Haes H. Psychometric qualities of the RAND 36-Item Health Survey 1.0: a multidimensional measure of general health status. *Int J Behav Med* 1996;3:104–122.

17. Consky E, Lang A. Clinical assessments of patients with cervical dystonia. In: Jankovic J, Hallett M, eds. *Therapy with Botulinum Toxin*. New York, NY: Marcel Dekker; 1994:211–237.

18. Guy W. The Clinical Global Impression scale. In: *ECDEU Assessment Manual for Psychopharmacology-Revised*. Rockville, MD, US: Department of Health, Education, and Welfare; Alcohol, Drug Abuse, and Mental Health Administration; National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:218.

19. Vidailhet M, Grabli D, Roze E. Pathophysiology of dystonia. *Curr Opin Neurol* 2009;22:406–413.

20. Smit M, Bartels AL, van Faassen M, et al. Serotonergic perturbations in dystonia disorders-a systematic review. *Neurosci Biobehav Rev* 2016;65:264–275.

21. Pavese N, Metta V, Bose SK, Chaudhuri KR, Brooks DJ. Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. *Brain* 2010;133:3434–3443.

22. Paus S, Gross J, Moll-Muller M, et al. Impaired sleep quality and restless legs syndrome in idiopathic focal dystonia: a controlled study. *J Neurol* 2011;258:1835–1840.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. The effect of psychoactive medication on FSS, ESS, and PSQI scores

Table S2. Influence of motor symptom severity on the FSS, ESS, and PSQI

doi:10.1002/mdc3.12459