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Johanna Junker

Brian D. Berman

James Hall

Deena W. Wahba

Valerie Brandt

See next page for additional authors

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Authors

Johanna Junker, Brian D. Berman, James Hall, Deena W. Wahba, Valerie Brandt, Joel S. Perlmutter, Joseph Jankovic, Irene A. Malaty, Aparna Wagle Shukla, Stephen G. Reich, Alberto J. Espay, Kevin R. Duque, Neepa Patel, Emmanuel Roze, Marie Vidailhet, H A. Jinnah, and Norbert Brüggemann

Original research

Quality of life in isolated dystonia: non-motor manifestations matter

Johanna Junker,[1,2] Brian D Berman ,[3] James Hall,[4] Deena W Wahba,[5] Valerie Brandt ,[6] Joel S Perlmutter,[7] Joseph Jankovic ,[8] Irene A Malaty,[9] Aparna Wagle Shukla ,[9] Stephen G Reich,[10] Alberto J Espay ,[11] Kevin R Duque,[11] Neepa Patel,[12] Emmanuel Roze,[13,14] Marie Vidailhet,[13,14] H.A. Jinnah,[15] Norbert Brüggemann [1,2,16]

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For numbered affiliations see end of article.

Correspondence to
MD Norbert Brüggemann, Department of Neurology and Institute of Neurogenetics, University of Luebeck, 23538, Luebeck, Schleswig-Holstein, Germany; norbert.brueggemann@neuro.uni-luebeck.de

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ABSTRACT

Objective To evaluate the relationship between health-related quality of life (HR-QoL) and both physical and psychiatric factors in a large, international, multicentre cohort of patients with isolated dystonia, the Dystonia Coalition.

Methods Natural history data from 603 patients with isolated dystonia (median age 57 years (IQR: 48 to 64 years), 67.0% women) were prospectively acquired and analysed. HR-QoL (RAND 36-Item Health Survey), severity of depressive symptoms, generalised anxiety (Hospital Anxiety and Depression Scale) and social anxiety (Liebowitz Social Anxiety Scale) were assessed. Dystonia severity (Burke-Fahn-Marsden Dystonia Rating Scale) and dystonic tremor were examined. Statistical predictors of HR-QoL were calculated using saturated path analysis.

Results Reduced HR-QoL was strongly associated with the degree of depressive symptoms and generalised and social anxiety (8/8 RAND 36 subscales, p≤0.001). Increased dystonia severity was associated with worse physical functioning, physical and emotional role functioning and social functioning (all p≤0.001). The presence of tremor correlated with worse physical functioning and pain (all p≤0.006). Younger age was associated with reduced emotional well-being and vitality (all p≤0.006). There were no HR-QoL differences between sexes.

Conclusion HR-QoL in isolated dystonia is strongly associated with psychiatric and physical features. While current standard of care focus on motor aspects of dystonia, comprehensive care should address both physical and mental aspects of health.

INTRODUCTION

Health-related quality of life (HR-QoL) is reduced in patients with dystonia compared with population-based samples.[1–4] HR-QoL in dystonia is not only determined by motor symptoms (MS) including dystonia severity and dystonic tremor but also by non-motor symptoms (NMS), that is, depression, anxiety, social phobia, low self-esteem and pain.[3 5] NMS are frequent in dystonia in comparison to population-based samples, which have an annual prevalence of 7% for depression,[6] 1% to 6% for generalised anxiety disorder (GAD)[7–9] and 2% to 8% for social anxiety disorder (SAD).[9 10] The point prevalence in dystonia is 16% to 48% for depression, 20% to 50% for GAD and 40% for SAD.[3 5 11–14] The relationship between MS and NMS is poorly understood, that is, to which extent NMS are secondary due to MS or a result of impaired neuronal processing.[15]

Previous studies in dystonia aimed to reveal the relationship of HR-QoL with MS and NMS.[15–17] Their significance, however, has been limited due to relatively small sample sizes and methodological differences, for example, between self-evaluation of dystonia severity versus rating of dystonia by an experienced investigator.[15–17] Thus, no systematic analysis of the influence of MS and NMS severity on HR-QoL has yet been performed in a comprehensive dystonia cohort. Here, we analysed data from the Dystonia Coalition cohort, a large prospectively investigated and international sample of patients with isolated dystonia, and hypothesised that psychiatric manifestations have a higher impact on HR-QoL than dystonia severity and tremor. Mental health of patients with dystonia and its overall burden on HR-QoL may not be well addressed since dystonia treatment mainly focusses on the motor aspects of the disease.

METHODS

Participants

The analysis included participants' data from baseline assessment of the Natural History Project of the Dystonia Coalition clinical database enrolled between 12 January 2011 and 3 November 2017 across 36 clinical sites (USA, Canada, Australia, Germany, France and Italy). Additional Dystonia Coalition investigators that contributed subjects to the study are listed in online supplemental file. The Dystonia Coalition is a multicentre study of patients with isolated dystonia, aged 18 years and older, and the Natural History Project includes patients with dystonia onset no more than 5 years prior to study enrolment (https://www.rarediseasesnetwork.org/cms/dystonia).

Participants answered a standardised questionnaire and were clinically examined using a standardised protocol. Patients with dystonia with botulinum toxin (BoNT) treatment were enrolled when symptoms returned. This usually meant they were enrolled 3 months after treatment, but

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never less than 2 months after treatment. Exclusion criteria were secondary and combined dystonia and medical/neurological conditions confounding diagnoses or precluding a complete assessment. For the current study a small group of patients with a confirmed mutation in a dystonia-related gene were excluded (n=12) as certain monogenic forms, for example, SGCE-related dystonia, exhibit a specific neuropsychiatric profile and are thus accompanied by a high burden of NMS.[18]

Classification of dystonia referring to body distribution was conducted according to Albanese *et al*.[19] Type of dystonia was divided into focal, segmental, multifocal and generalised dystonia. Focal dystonia was further divided into blepharospasm, oromandibular/lingual, laryngeal, cervical and limb dystonia.

Standard protocol approvals and patient consents

All participants gave written informed consent for study participation prior to study enrolment.

Questionnaire and rating scales

HR-QoL and NMS were evaluated by generic, validated and widely used rating scales (RAND 36-Item Health Survey, Hospital Anxiety and Depression Scale, Liebowitz Social Anxiety Scale) to allow for comparison with other dystonia and movement disorder studies.[20–22]

Dystonia Coalition Questionnaire

Demographic and clinical data included sex, age, affected body regions, the presence of other movement disorders including tremor, age at onset, disease duration, medical treatment for dystonia, medical history and mutations in dystonia-related genes.

RAND 36-Item Health Survey

HR-QoL was evaluated using the RAND 36-Item Health Survey 1.0. The RAND 36 is a generic quality of life questionnaire to measure physical and mental well-being, relies on patient self-reporting and was developed in the Medical Outcome Study.[20] It contains 36 questions representing the following eight subscales: general health, physical functioning, role limitations due to physical health problems, pain, energy/fatigue, emotional well-being, role limitations due to emotional problems and social functioning. The questions are rated on a Likert scale with up to six response options and seven questions are answered with yes or no. Original response categories are recoded to values of a 0% to 100% range and the items of each of the eight subscales are averaged. A high score represents a better health state. The RAND 36-Item Health Survey 1.0 and the 36-Item Short Form Survey (SF-36) include the same items, while the scoring algorithm is different regarding the general health and pain scales.[23] The scoring algorithm of the RAND 36-Item Health Survey 1.0 was used in this study.

Hospital Anxiety and Depression Scale

Severity of generalised anxiety and depressive symptoms was assessed by the self-reported Hospital Anxiety and Depression Scale (HADS) V.4.[21] Each of the two subscales (HADS-A and HADS-D) contain seven questions rated on a 4-point scale (0 to 3), each subscale yielding score ranging from 0 to 21. Standard scale cut-offs indicated the presence of depression and anxiety (HADS-A >7 and HADS-D >7).

Liebowitz Social Anxiety Scale

The self-reported Liebowitz Social Anxiety Scale (LSAS) is a 24-item scale divided into two subscales assessing fear/anxiety concerning performance and pertaining to social situations as well as avoidance behaviour.[22] The 24 items of the two subscales are rated on a Likert scale from 0 to 3 yielding a maximum sum score of 144. The presence of social anxiety was indicated by a standard scale cut-off >30.

Examination protocol and rating

Standardised examination of all patients included evaluation of eyes, mouth, tongue, neck, arms, hands, legs and feet and the examination of speech, voice, swallowing, handwriting, standing and walking.[24] A movement disorder neurologist evaluated dystonia severity across different body regions using the validated Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS).[25] Tremor was assessed by observing all body regions for the occurrence of tremor regardless of its amplitude, frequency or regularity. The BFMDRS evaluates provoking (scale 0 to 4) and severity factors (scale 0 to 4) of nine different body parts (eyes, mouth, speech/swallowing, neck, right arm, left arm, right leg, left leg, trunk). For each body part, provoking factor, severity factor and a weight factor (0.5 or 1) were multiplied yielding score ranges from 0 to 120, with higher scores indicating more severe dystonia.

Statistical analysis

To analyse the relationship between MS and NMS with HR-QoL, simultaneously estimated bivariate correlations were obtained from a saturated path analysis performed in MPlus V.7.4.[26] The eight subscales of the RAND 36-Item Health Survey, the three NMS scores (HADS-D, HADS-A and LSAS), and the two MS factors (BFMDRS and tremor (yes/no)) were entered into the model, as well as age and sex to control for their effects. The Full Information Maximum Likelihood statistical procedure was used for replacement of missing values in the path analysis that was undertaken. Bonferroni-corrected alphas were calculated to adjust for multiple comparisons (simultaneous correlations), and p values ≤0.006 were considered significant.

Differences regarding the severity of NMS between patients with and without antidepressants were assessed using t-tests for independent samples. All tests of significance were two-sided. Bonferroni-corrected alphas ≤0.017 were considered significant.

Data availability

Anonymised data (study protocol and statistical analysis) will be shared by request from any qualified investigator. Data will be available for 10 years.

RESULTS

Out of 615 participants, 12 were excluded due to secondary or combined dystonia or a confirmed mutation in a dystonia-related gene. Of the remaining 603 patients with isolated dystonia, 1.5% of data points were missing.

The majority of patients were women (67.0%, 404/603). The median age at baseline examination was 57 years (IQR: 48 to 64 years), and the median age at dystonia onset 54 years (IQR: 45 to 61 years). Table 1 displays mean BFMDRS scores, the ratio of patients with tremor, mean total scores of RAND 36-Item Health Survey, HADS-D, HADS-A and LSAS as well as the ratio of patients with symptoms of a depression (HADS-D >7), GAD (HADS-A >7) and SAD (LSAS >30). In detail, symptoms of

Table 1 Clinical data of the study cohort

	HR-QoL	Depression	Generalised anxiety	Social anxiety	BFMDRS	Tremor
All (n=603)	63.6±21.8	21.5% (127/591) 4.6±4.0	36.7% (217/591) 6.4±4.2	44.3% (262/591) 32.1±26.0	6.7±5.0	43% (259/603)
Main groups of dystonia						
Focal (n=373)	66.3±21.8	20.0 % (73/365) 4.4±4.0	37.3 % (136/365) 6.4±4.1	41.5% (152/366) 30.9±25.4	4.4±2.4	44.0 % (164/373)
Segmental (n=171)	58.0±21.0	24.6% (41/167) 5.4±4.1	36.5 % (61/167) 6.7±4.2	55.1% (92/167) 36.8±26.7	9.8±5.3	39.8% (68/171)
Multifocal (n=49)	64.4±20.9	20.4% (10/49) 3.9±3.3	30.6% (15/49) 5.3±4.2	30.6% (15/49) 25.9±24.7	9.5±4.4	42.9% (21/49)
Generalised (n=10)	58.1±24.9	30% (3/10) 5.0±4.4	50% (5/10) 7.3±5.3	33.3% (3/9) 29.4±34.3	21.4±9.4	60% (6/10)
Subgroups of focal dystonia						
Blepharospasm (n=41)	70.8±20.3	19.5% (8/41) 4.3±4.2	24.4% (10/41) 5.3±4.1	19.5% (8/41) 24.2±25.8	4.6±2.3	14.6 % (6/41)
Oromandibular/lingual (n=22)	67.7±19.9	18.2% (4/22) 4.7±4.0	22.7% (5/22) 5.5±3.5	36.4% (8/22) 27.9±20.0	3.8±3.0	27.3% (6/22)
Laryngeal (n=30)	77.1±15.6	13.3% (4/30) 3.1±3.1	46.7% (14/30) 7.8±4.3	66.7% (20/30) 40.7±23.6	3.1±1.8	33.3% (10/30)
Cervical (n=227)	62.3±22.6	23.2% (51/220) 4.7±4.1	41.8% (92/220) 6.8±4.2	45.0% (99/220) 33.1±26.8	4.7±2.3	57.3% (130/227)
Limb (n=53)	73.1±18.9	11.5% (6/52) 3.4±3.3	28.8% (15/52) 5.4±3.3	32.1% (17/53) 22.8±17.8	3.8±2.5	22.6% (12/53)

HR-QoL and BFMDRS: Mean RAND 36-Item Health Survey total scores (range 0% to 100%) and mean BFMDRS scores with SD of all patients and per type of dystonia.
Depression, GAD and SAD: Percentage and numbers of patients with symptoms of depression (HADS-D > 7), GAD (HADS-A > 7), SAD (LSAS > 30) and mean HADS-D, mean HADS-A and mean LSAS scores with SD of all patients and per type of dystonia.
Tremor: Percentage and numbers of patients with dystonic tremor of all patients and per type of dystonia.
BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; GAD, generalised anxiety disorder; HADS, Hospital Anxiety and Depression Scale; HR-QoL, health-related quality of life; LSAS, Liebowitz Social Anxiety Scale; SAD, social anxiety disorder.

depression were found in 22%, symptoms of GAD in 37% and SAD in 44% of patients.

With regard to therapy, 68.0% (410/603) were treated with BoNT, 39.5% (238/603) with oral anti-dystonic drugs (anticholinergics, benzodiazepines, non-benzo hypnotics, dopaminergics, antidopaminergics and muscle relaxants) and 19.1% with antidepressants. The group of patients with antidepressants (depression: 6.3±4.3 vs 4.2±3.8 (M±SD), t(589) = −5.1, p<0.000; GAD: 8.2±4.2 vs 6.0±4.0 (M±SD), t(589) = −5.3, p<0.000; SAD: 38.6±30.0 vs 30.6±24.7 (M±SD), t(589) = −3.0, p=0.003) exhibited higher depression and anxiety scores. None of the patients had deep brain stimulation, whereas 0.8% of patients had previously received other surgical treatment for dystonia (myectomy for blepharospasm or spasmodic dysphonia (n=3), selective denervation for cervical dystonia (n=2)).

Influence of MS and NMS on HR-QoL in dystonia

The results of the path analysis with numerical estimates as indicators of the strength of the relationships between the eight HR-QoL subscales (RAND 36-Item Health Survey) and dystonia severity (BFMDRS), tremor, severity of depressive symptoms (HADS-D), GAD (HADS-A) and SAD (LSAS), as well as age at examination and sex are displayed in table 2 and figure 1. Lower HR-QoL of all eight subscales related to more severe depressive symptoms, GAD and SAD (all p≤0.001). Depressive symptoms presented with highest (−0.47 up to −0.72) and social anxiety with lowest estimates (−0.23 up to −0.42). Higher dystonia severity was associated with lower physical functioning, physical and emotional role functioning and social functioning (all p≤0.001), and the presence of tremor was associated with lower HR-QoL regarding physical functioning and pain (all p≤0.006). Both dystonia severity and tremor presented low estimates (−0.09 up to −0.24). Younger age was associated with reduced emotional well-being and vitality (all p≤0.006, estimates 0.13 to 0.15). Sex was not associated with any differences in HR-QoL subscales.

DISCUSSION

Symptoms of depression, GAD and SAD are related to worse HR-QoL in patients with dystonia in the large international Dystonia Coalition cohort. We found an additional association of HR-QoL with dystonia severity, tremor and age at examination. Twenty per cent of our patients were treated with antidepressants. The degree of underlying depressive symptoms and anxiety may thus have been underestimated.

Table 2 Simultaneously estimated bivariate correlations obtained from a saturated path analysis

Health-related quality of life subscale	Dystonia severity	Tremor	Depression	Generalised anxiety	Social anxiety	Age	Sex
General health	−0.09 (−0.17 to −0.01)	−0.05 (−0.13 to 0.03)	−0.50*** (−0.57 to −0.44)	−0.40*** (−0.47 to −0.33)	−0.31*** (−0.39 to −0.22)	0.07 (−0.01 to 0.15)	−0.04 (−0.12 to 0.04)
Physical functioning	−0.14*** (−0.22 to −0.06)	−0.14*** (−0.22 to −0.06)	−0.47*** (−0.54 to −0.4)	−0.27*** (−0.35 to −0.18)	−0.27*** (−0.36 to −0.18)	−0.07 (−0.15 to 0.01)	−0.07 (−0.15 to 0.002)
Physical role functioning	−0.24*** (−0.32 to −0.16)	−0.01 (−0.09 to 0.07)	−0.49*** (−0.55 to −0.43)	−0.35*** (−0.42 to −0.28)	−0.26*** (−0.34 to −0.2)	0.08 (0.003 to 0.16)	−0.06 (−0.14 to 0.02)
Pain	−0.10 (−0.19 to −0.001)	−0.11** (−0.19 to −0.03)	−0.52*** (−0.58 to −0.45)	−0.38*** (−0.46 to −0.31)	−0.23*** (−0.32 to −0.14)	0.11 (0.03 to 0.2)	−0.07 (−0.15 to 0.01)
Energy/fatigue	−0.09 (−0.17 to −0.01)	−0.09 (−0.18 to −0.01)	−0.66*** (−0.71 to −0.61)	−0.45*** (−0.51 to −0.38)	−0.34*** (−0.41 to −0.27)	0.13** (0.05 to 0.21)	−0.05 (−0.13 to 0.03)
Emotional well-being	−0.11 (−0.2 to −0.02)	−0.002 (−0.08 to 0.08)	−0.72*** (−0.76 to −0.67)	−0.68*** (−0.72 to −0.63)	−0.41*** (−0.49 to −0.33)	0.15*** (0.07 to 0.22)	0.01 (−0.07 to 0.09)
Emotional role functioning	−0.17*** (−0.26 to −0.09)	0.02 (−0.06 to 0.1)	−0.49*** (−0.56 to −0.42)	−0.42*** (−0.48 to −0.35)	−0.32*** (−0.4 to −0.24)	0.11 (0.03 to 0.19)	0.01 (−0.07 to 0.09)
Social functioning	−0.23*** (−0.32 to −0.15)	−0.004 (−0.09 to 0.08)	−0.67*** (−0.72 to −0.62)	−0.44*** (−0.5 to −0.37)	−0.42*** (−0.5 to −0.35)	0.10 (0.02 to 0.18)	0.05 (−0.03 to 0.14)

Path analysis: Numerical estimates and 95% CIs as indicators of the strength of the relationships between the eight HR-QoL subscales (RAND 36-Item Health Survey) and dystonia severity (BFMDRS), tremor, severity of depression (HADS-D), severity of generalised anxiety (HADS-A), severity of social anxiety (LSAS), age and sex in 603 patients with dystonia.
** Bonferroni corrected alpha ≤ 0.006; ***$p \leq 0.001$
BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; HADS, Hospital Anxiety and Depression Scale; HR-QoL, health-related quality of life; LSAS, Liebowitz Social Anxiety Scale.

Our results are in keeping with previous studies in smaller samples of patients with dystonia, which have already indicated that depression, GAD, low self-esteem, embarrassment and acceptance of illness are important determinants of HR-QoL.[3 16 17 27 28] Motor severity was, however, not as strongly associated with HR-QoL in our study. The weaker association with motor severity may be due to the fact that we used the BFMDRS to assess dystonia severity which is a validated[25] and commonly used rating scale but it may not be sensitive enough for focal dystonias. In keeping with this notion, most patients had focal or segmental dystonia in our sample whereas generalised (10/603) and multifocal (49/603) dystonias were less common. Other studies have also found a stronger relationship of QoL with NMS than with MS but this may again be attributable to the heterogeneity of dystonia subtypes in different cohorts and especially in those with smaller sample sizes and the use of different rating scales (BFMDRS, TWSTRS, Tsui score, UDRS).[3 11 27] Furthermore, the examination of patients under BoNT treatment at different time intervals limits the comparability of results. Of note, almost 70% of our patients were treated with BoNT about 3 months prior to the examination, indicating that dystonia severity may have been potentially higher in some patients without long-term BoNT therapy[29] and may have resulted in stronger associations with lower HR-QoL. Thus, it is conceivable that the impact of MS severity in our and previous studies may be lessened by the availability and ongoing utilisation of effective treatments as BoNT and deep-brain stimulation with positive long-term effects on HR-QoL,[3 30]

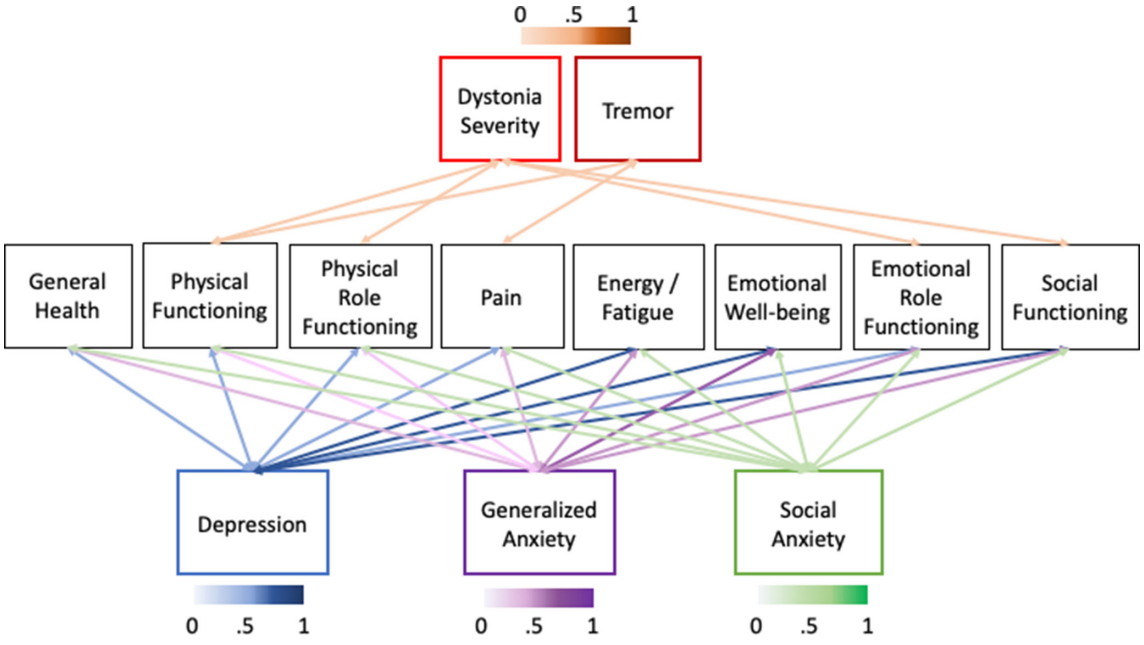

Figure 1 Simultaneously estimated bivariate correlations obtained from a saturated path analysis. Stylised illustration to demonstrate the strength of the relationships between the eight HR-QoL subscales (RAND 36-Item Health Survey) and dystonia severity (BFMDRS), tremor, severity of depression (HADS-D), severity of generalised anxiety (HADS-A), severity of social anxiety (LSAS) in 603 patients with dystonia. BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; HADS, Hospital Anxiety and Depression Scale; HR-QoL,health-related quality of life; LSAS, Liebowitz SocialAnxiety Scale.

as compared with the potentially less uniform implementation of treatments for the NMS. MS and MS-related pain should of course be treated to improve and stabilise HR-QoL.[31–35]

Dystonic tremor is a frequent clinical sign in dystonia[36] and tremor is a source of reduced QoL in other tremor types.[37] The impact of dystonic tremor on HR-QoL in patients with dystonia has previously not been sufficiently addressed. We found that dystonic tremor was negatively associated with physical functioning and pain-related QoL. Although patients were evaluated as symptoms returned after BoNT treatment, a sustained improvement in patients with long-term BoNT therapy cannot be excluded. Therefore, investigations of patients who are BoNT-naive may reveal even stronger associations. Our results implicate the importance of treating dystonic tremor to improve HR-QoL.

Population-based studies illustrate age-dependent and sex-dependent prevalence of psychiatric conditions with a decrease in people >50 years of age and women being more anxious.[6–8] Controlling our analysis for age and sex, HR-QoL in patients with dystonia did not differ between men and women, while younger age in dystonia was associated with reduced emotional well-being and vitality.

The question of whether NMS are a primary phenomenon of the disease or a secondary response to physical impairment remains unanswered.[15] In dystonia as well as in Parkinson's disease the most potent predictors of HR-QoL appear to be depression and anxiety.[38 39] An increased risk of recurrent major depressive episodes in manifesting and non-manifesting *TOR1A* mutation carriers argues for a primary phenomenon,[40] while higher depression and anxiety scores in symptomatic but not in asymptomatic *SCGE* carriers may argue for this to be a secondary epiphenomenon with the limitation that in most SGCE carriers the mutated allele will be silenced.[41] Recent reports of familial coaggregation of psychiatric comorbidities in dystonia and an impaired theory of mind in cervical dystonia support shared genetic factors.[42 43] High prevalences of social anxiety in dystonia and QoL predictors as low self-esteem, self-deprecation and educational level in cervical dystonia[16] point towards an impact of MS on HR-QoL although for most dystonias there may be a bidirectional and dynamic relationship between MS and NMS.[15]

Our study has certain limitations: The size of the cohort allows for drawing meaningful conclusions, even while controlling for important confounders, such as sex and age. Nevertheless further factors such as educational level, marital and socioeconomic status may significantly influence HR-QoL and were not assessed to guarantee statistical power.

A considerable proportion of patients were treated with oral anti-dystonic drugs and/or antidepressants. Their influence on NMS was not controlled for because the mechanism of action strongly varies across drug classes and some patients received medication from more than one drug class and with different dosages. Given the different drug targets and the contradictory or independent mechanisms (eg, dopaminergics vs anti-dopaminergics or anti-dystonic vs anti-depressive effects) as well as the co-medication in several patients we refrained from a combined analysis. One of the inclusion criteria was disease duration less than 5 years, which prevented the assessment of later disease stages. Another limitation of our study is that only carriers of known mutations in dystonia-related genes were excluded but that no systematic screening was performed. Furthermore, new genes may not have yet been identified at the time point of the study, for example, VPS16 which was very recently described in the context of dominantly inherited isolated dystonia.[44] The rationale to exclude patients with a monogenic background was to account for a potential confounder as they may present with a distinct neuropsychiatric profile and a different burden of NMS. The mutation frequency is, however, very low in isolated dystonia cases whereas the likelihood to identify causative mutations is considerably higher in combined or complex dystonias as previously shown in a large dystonia sample where exome sequencing was performed.[45 46] Further, mutations in dystonia-related genes are enriched in generalised or multifocal dystonia although it can be very rarely found in patients with focal dystonias. As most patients in our sample suffered from focal dystonia (62%) we thus assume that the number of unidentified mutations will be relatively low. The BFMDRS is a validated[25] and commonly used rating scale for dystonia but it may not be sensitive enough for focal dystonias. Furthermore, dystonic tremor is an important clinical feature that is not well reflected in currently used clinical scales. Accordingly, the qualitative assessment in this study (tremor yes/no) is no longer appropriate to account for the specific features of dystonic tremor including distribution in different body regions, frequency, amplitude, regularity in frequency and amplitude and alleviating or provoking manoeuvres. Another prerequisite is the sensitivity of a clinical rating scale to change, for example, due to treatment. This is reflected by a recent paper showing that the diagnosis of dystonic tremor is still problematic because of different opinions on its very definition even across experts.[47]

HR-QoL in isolated dystonia is strongly associated especially with NMS as well as less related to MS, while standard therapy regimens only concentrate on the physical symptoms. Comprehensive care of patients with dystonia should address both physical and mental health and aim to improve acceptance of the disease and coping strategies.

Author affiliations
[1]Department of Neurology, University of Luebeck, Luebeck, Germany
[2]Institute of Neurogenetics, University of Luebeck, Luebeck, Germany
[3]Department of Neurology, Virginia Commonwealth University, Richmond, VA, USA
[4]Southampton Education School, University of Southampton, Southampton, UK
[5]BayCare Laboratories, BayCare Health Systems, Tampa, FL, USA
[6]School of Psychology, Centre for Innovation in Mental Health, University of Southampton, Southampton, UK
[7]Departments of Neurology, Radiology, Neuroscience, Physical Therapy & Occupational Therapy, Washington University in St. Louis, St. Louis, MO, USA
[8]Parkinsons' Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA
[9]Department of Neurology, Fixel Institute for Neurologic Disorders, University of Florida, Gainesville, Florida, USA
[10]Department of Neurology, University of Maryland, School of Medicine, Baltimore, MD, USA
[11]Department of Neurology, University of Cincinnati, Cincinnati, OH, USA
[12]Department of Neurology, Henry Ford Hospital West Bloomfield, West Bloomfield, MI, USA
[13]Departement de Neurologie, AP-HP, Hopital de la Pitie-Salpetriere, Paris, France
[14]Institut du Cerveau_Paris Brain Institute-ICM, INSERM 1127, CNRS 7225, Sorbonne Universités, Paris, France
[15]Department of Neurology and Human Genetics, Emory University, Atlanta, GA, USA
[16]Center of Brain, Behavior and Metabolism, University of Luebeck, Luebeck, Germany

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Contributors JJ, acquisition of data, study concept and design, analysis and interpretation of data, drafting of manuscript; JH, statistical analysis, critical revision of manuscript for intellectual content; VB, statistical analysis, critical revision of manuscript for intellectual content; BDB, DW, JSP, JJ, IAM, AWS, SGR, AJE, KRD, NP, ER, MV and HAJ acquisition of data, critical revision of manuscript for intellectual content; NB, study concept and design, analysis and interpretation of data, study supervision, critical revision of manuscript for intellectual content; Statistical Analysis conducted by JH and VB.

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Dr Perlmutter serves as Director of Medical and Scientific Advisory Committee of the Dystonia Medical Research Foundation, Chair of the Scientific Advisory Committee of the Parkinson Study Group, Chair of the Standards Committee of the Huntington Study Group, member of the Scientific Advisory Board of the APDA, Chair of the Scientific and Publication Committee for ENROLL-HD and member of the Education Committee of the Huntington Study Group. JJ has received research/training funding from: AbbVie Inc; Acadia Pharmaceuticals; Allergan, Inc; Biotek; Cerevel Therapeutics; CHDI Foundation; Dystonia Coalition; Emalex Biosciences, Inc; F Hoffmann-La Roche Ltd; Huntington Study Group; Medtronic Neuromodulation; Merz Pharmaceuticals; Michael J Fox Foundation for Parkinson Research; National Institutes of Health; Neuraly, Inc; Neurocrine Biosciences; Parkinson's Foundation; Parkinson Study Group; Prilenia Therapeutics; Revance Therapeutics, Inc; Teva Pharmaceutical Industries Ltd. 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Reports receiving honoraria from Acadia, Cavion, Elsevier and MJFF in past; Participates as a co-I for several NIH, foundation and industry sponsored trials over the years but has not received honoraria. SGR has active or recent grant support from NINDS and royalties from Springer and Informa. He has also served as a consultant for Best Doctors and as a reviewer for UpToDate. He serves on the Data Safety Monitoring Board for Enterin. AJE has received grant support from the NIH and the Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for AbbVie, Neuroderm, Neurocrine, Amneal, Adamas, Acadia, Acorda, InTrance, Sunovion, Lundbeck, and USWorldMeds; publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer; and honoraria from USWorldMeds, Acadia, and Sunovion; NP has received honoraria as a speaker for USWorldMed and Teva and consultant for Revance and Acorda pharmaceutical. 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He also is principle investigator for the Dystonia Coalition, which has received the majority of its support through the NIH (grants NS116025, NS065701 from the National Institutes of Neurological Disorders and Stroke TR 001456 from the Office of Rare Diseases Research at the National Center for Advancing Translational Sciences). The Dystonia Coalition has received additional material or administrative support from industry sponsors (Allergan Inc and Merz Pharmaceuticals) as well as private foundations (The American Dystonia Society, Beat Dystonia, The Benign Essential Blepharospasm Foundation, Cure Dystonia Now, Dystonia Europe, Dystonia Inc, Dystonia Ireland, The Dystonia Medical Research Foundation, The Foundation for Dystonia Research, The National Spasmodic Dysphonia Association and The National Spasmodic Torticollis Association). NB received speaker's honoraria from Grünenthal, UCB, AbbVie and Teva. He served as consultant for Censa and Centogene. 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ORCID iDs
Brian D Berman http://orcid.org/0000-0002-0602-9942
Valerie Brandt http://orcid.org/0000-0002-3208-2659
Joseph Jankovic http://orcid.org/0000-0003-2977-9743
Aparna Wagle Shukla http://orcid.org/0000-0001-7139-3647
Alberto J Espay http://orcid.org/0000-0002-3389-136X
Norbert Brüggemann http://orcid.org/0000-0001-5969-6899

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