Motor and non-motor determinants of health-related quality of life in young dystonia patients

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ABSTRACT

Objectives: To systematically investigate the relationship between motor and non-motor symptoms, and health-related quality of life (HR-QoL) in children and young adults with dystonia.

Methods: In this prospective observational cross-sectional study, 60 patients (6-25 years) with childhood-onset dystonia underwent a multidisciplinary assessment of dystonia severity (Burke-Fahn-Marsden Dystonia Rating Scale, Global Clinical Impression), motor function (Gross Motor Function Measure, Melbourne Assessment of Unilateral Upper Limb Function), pain (visual analogue scale), intelligence (Wechsler Intelligence Scale), executive functioning (Behavior Rating Inventory of Executive Function) and anxiety/depression (Child/Adult Behavior Checklist). Measures were analyzed using a principal component analysis and subsequent multiple regression to evaluate which components were associated with HR-QoL (Pediatric Quality of life Inventory) for total group, and non-lesional (primary) and lesional (secondary) subgroups.

Results: Patients (29 non-lesional, 31 lesional dystonia) had a mean age of 13.6 ± 5.9 years. The principal component analysis revealed three components: 1) motor symptoms; 2) psychiatric and behavioral symptoms; and 3) pain. HR-QoL was associated with motor symptoms and psychiatric and behavioral symptoms (R^2=0.66) for the total sample and lesional dystonia, but in the non-lesional dystonia subgroup only with psychiatric and behavioral symptoms (R^2=0.51).

Conclusions: Non-motor symptoms are important for HR-QoL in childhood-onset dystonia. We suggest a multidisciplinary assessment of motor and non-motor symptoms to optimize individual patient management.

KEY WORDS: dystonia; quality of life; non-motor symptoms; motor symptoms; psychiatric

INTRODUCTION

Dystonia is a hyperkinetic movement disorder in which sustained or intermittent muscle contractions cause abnormal, often repetitive, movements, postures or both.[1] In contrast to the mainly idiopathic adult-onset dystonias, childhood dystonia can be caused by a broad spectrum of etiologies, the most common being cerebral palsy (CP).[2] In addition, multiple heritable causes are known.[3] The wide variety in etiology gives rise to a heterogeneous patient population with isolated dystonia or dystonia as part of a complex clinical picture with co-existent movement disorders or (non-)neurological features (for example spasticity, epilepsy, dysmorhpias, deafness, developmental delay). The dystonia classification system enables clinicians to categorize patients.[1] Patients are frequently clustered according to etiology, with idiopathic and secondary as main groups.[4] Idiopathic or hereditary dystonia patients with no evidence of brain damage are referred to as non-lesional dystonia. In addition, there are secondary or lesional dystonias with a cluster including progressive dystonia (with neurodegeneration) and static dystonia (associated with structural lesions).

There is growing interest in non-motor features, such as depression, anxiety, pain and selective cognitive impairments (e.g. executive functioning), and their impact on the lives of patients.[5] For instance, in adult-onset cervical dystonia patients depression or pain have been shown to be more important predictors of the health-related quality of life (HR-QoL) than dystonia severity.[6,7] Despite these findings, information relating to the impact of non-motor symptoms in children and young adults with dystonia is still lacking.

We therefore performed a systematic multidisciplinary assessment of sixty patients with dystonia due to different etiologies. The aim was to explore to what extent motor and non-motor symptoms are related to HR-QoL, and to evaluate if the contribution of these symptoms differed between patients with non-lesional and lesional dystonia.

METHODS

Participants

This cross-sectional study included a total of 60 consecutive referred children and young adults with a clinical diagnosis of dystonia. Inclusion criteria were 1) an age between 6 and 26 years, based on the minimal and maximal age for several outcome measures, and 2) childhood-onset dystonia diagnosed by a movement disorders expert. To keep the sample representative, the only exclusion criterion was a language barrier between the team and patient and/or caregivers.

Most patients (45) were referred to our dystonia team after visiting the specialized multidisciplinary outpatient clinic for movement disorders at the University Medical Center Groningen. In addition, fifteen patients were referred from the (pediatric) neurology and rehabilitation outpatient clinics. Informed consent or assent was obtained for all participants and the study was approved by the local ethics committee (M13.132238).

Sample size calculation was based on a pilot in fifteen patients. Dystonia severity (measured with the Burke-Fahn-Marsden dystonia rating scale, BFMDRS) was the least important predictor of HR-QoL with a medium effect size. G*Power was used to calculate that to detect an effect size of 0.4 with a power of 0.8 (1-β), 52 patients needed to be included. With a drop-out of 10-15%, this led to a sample size of 60 in total.[8]

Multidisciplinary team members and evaluation

The team consists of clinicians and allied health professionals within the departments of neurology, neuropsychology and rehabilitation, i.e.. neurologists, neuropsychologists, rehabilitation doctor, physiotherapist and occupational therapists. Patients visited our hospital for a one or two-day systematic multidisciplinary evaluation. This evaluation comprised questionnaires regarding HR-QoL, mood, behavior and executive functioning. In addition,

quantitative standardized tests were undertaken to evaluate dystonia severity, gross and fine motor function and cognition.

Outcome measures

Symptom severity

Severity of dystonia was determined using the motor subscale of the BFMDRS.[9] Two experts (DS, KP) video-rated dystonia extent in nine body regions (eyes, mouth, speech/swallowing, neck, upper extremities, trunk and lower extremities) and the total sum score was determined.

The Clinical Global Impression Scale (GCI-S) was also used to rate the severity of motor symptoms from normal (1) to extremely impaired (7).[10] The rater scored the GCI-S on the total clinical picture, including dystonia and potential co-existent symptoms.

Motor functioning

The Gross Motor Function Measure (GMFM-88) was used for the measure of gross motor abilities in five settings (lying and rolling, sitting, crawling and kneeling, standing, and walking, running and jumping).[11] In a normally developing child, all items can be executed at the age of 5.5 years. The test were carried out by a qualified physiotherapist, and the total overall score was used for analysis.

The arm function was measured using the Melbourne Assessment of Upper Limb Function (MAULLF) administered by an occupational/hand therapist (RT, ME).[12] This test measures the movement range, accuracy, dexterity and fluency of gross and fine motor movements separately for each arm, recorded as an overall percentage value (0-100). The mean value of the percentages in each arm was used as the overall score.

Pain

Pain was assessed using the Numeric Pain Rating Scale (NPRS) on the overall level of pain ranging from 0 (no pain) to 10 (worst imaginable pain).[13] When pain was present in more than one body area, an average pain score was derived.

Mood and anxiety

The presence of depressive and anxiety symptoms was measured with the Child Behavior Checklist (CBCL) or Adult Behavior Checklist (ABCL) completed by parents.[14,15] These are widely used to identify a broad spectrum of behavioral problems. The internalizing problems scale comprises symptoms related to somatic complaints, anxiety, depression and social withdrawal related behavior. Scores are given as a normative t-score, in which a score of 50-65 was normal range, 65-70 borderline and >70 clinically symptomatic.

Intelligence quotient

Intelligence quotient (IQ) was measured with the Wechsler Intelligence Scale for Children (WISC-III-NL) or Wechsler Adult Intelligence Scale (WAIS-III-NL).[16,17] Full IQ comprises verbal (general knowledge, language, reasoning, and memory skills) and performance scores (spatial, sequencing, and problem-solving skills). IQ was scaled as gifted (≥130), very high (120-129), bright normal (110-119), average (90-109), low-average (85-89), borderline (70-84), mental retardation or intellectual disability (<70).

Executive functioning

The Behavior Rating Inventory of Executive Function (BRIEF) is a widely used behavior rating scale.[18] It aims to identify potential executive deficits in the fields of inhibition, flexibility, emotional control, initiation, working memory, planning and organization, organization of materials, and monitoring. The summary score serves as an indicator of global executive functioning and was used for analysis. Scores are given as a normative t-score within the normal (50-65), borderline (65-70) or clinical range (>70).

Health-related quality of life

The Dutch Generic Core Scale of the Pediatric Quality of Life Inventory 4.0 (PedsQL) was used to determine HR-QoL.[19,20] This validated 23-item, age-adjusted questionnaire asks parents to indicate difficulties with physical activity (walking, running, exercise, lifting, self-care, pain, fatigue), emotion (anxiety, sadness, angriness, sleep, worrying), social interaction (getting along, friends, teasing, keeping up with others, playing) and school-related domains (attention, memory, schoolwork, missing school) over the past four weeks. Total HR-QoL score comprised the mean score the sum of all answers divided by the number of answered items and psychosocial functioning was calculated in the same way as for the emotional, social and social subscales.

Statistical analysis

The statistical analysis of the data was conducted using the PASW 23 Statistics for Windows (SPSS Statistics, Chicago, IL, USA) with significance threshold of $p < 0.05$. After testing for normal distributions with a Q-Q plot and a Shapiro-Wilk test, distribution was presented as mean and standard deviation (SD) or median and interquartile range (IQR) where appropriate.

Patients were divided into two subgroups according to the underlying etiology.[1,4] In order to increase the readability of the manuscript, we chose to use the terms non-lesional (primary) and lesional (secondary) dystonia. The idiopathic or hereditary dystonia patients without evidence of brain damage were referred to as non-lesional dystonia. To prevent overly small subgroups, children and young adults with dystonia due to static lesions or neurodegeneration, both hereditary and acquired, were categorized as lesional dystonia. Differences in patient characteristics were analyzed using the Pearson Chi-square test or Fisher's exact test or Mann-Whitney U.

HR-QoL was compared to a sample of healthy Dutch children published previously.[20] To determine predictors of HR-QoL, a principal component analysis (PCA)

and subsequent multiple regression analysis was performed. The PCA is an approach to reduce the dataset to a manageable size while retaining as much of the original data.[21] By looking at associations between variables, the PCA converts initial variables into clusters of correlated variables, so-called components. To compensate for potentially correlating components, we applied oblique component rotation. Because PCA is a method that explores (co)variance, outcome measures were normalized to z-scores before entering the PCA to enable direct comparison. Internal consistency of the components was adequate if Cronbach's Alpha >0.7. To check the robustness of the results and the possible influence of missing data, a sensitivity analysis with PCA was performed both with excluding cases list wise and pair wise to see if it resulted in the same components.

For each component derived from the PCA, bootstrapping was conducted as sensitivity analysis to test stability of the distribution (see supplement 1). Subsequently, a multiple regression with backward elimination was used to calculate to what extent the components explained variance in HR-QoL (total PedsQL score). The multiple regression was performed for the overall cohort, and the non-lesional and lesional dystonia subgroups independently.

RESULTS

Patient characteristics

The sixty patients (35M/25F) had a mean age at examination of 13.6 years (SD=5.9) and a motor disease duration of 9.6 years (SD=5.1) (Table 1). Fifteen patients were over the age of 18. The majority had a generalized dystonia (60%), followed by segmental (28%) and hemi dystonia (12%). In 25 patients, there was a mixed movement disorder with dystonia as main feature. Co-existent neurological or systemic features were present in 34 patients. A genetic etiology was identified in 23 patients, involving DYT4 (n=1), DYT6 (n=2), DYT11 (n=9),

DYT12 (n=1), Aristaless related homeobox gene (n=1), beta-actin gene (n=1), glutaric aciduria type 1 (n=2), Rett syndrome (n=1), methylmalonic acidemia (n=1), RELN (n=2), vitamin E deficiency (n=1) and uniparental disomy of chromosome 7 (n=1).

Dividing our sample revealed 29 non-lesional and 31 lesional dystonia patients. Characteristics differed between groups, with an earlier disease onset (1.5 vs 6.7 years), more generalized dystonia (71% vs 48%) and more frequent coexistent neurological or systemic features (77% vs 38%) in lesional dystonias.

Outcome measures

An overview of the outcome measures is presented in Table 2. Dystonia severity (median BFMDRS 38.4, IQR 23.8-90.0) and motor functioning (GMFM median 90% IQR 59.1-100%; MAULLF median 80.5% IQR 47.9-98.3%) varied among patients. For non-motor outcomes, median pain rate was 4.0 and 33% reported a moderate to severe level of pain (>5). Mean IQ score was 88.4 with an intellectual disability in 45% (n=27) of the patients. Twenty-one patients had borderline to clinical t-score on the internalizing problems scale of the CBCL and four elevated scores on the BRIEF, indicative of executive deficits.

Missing data on motor tests in Table 2 was because of fatigue or behavioral aspects interfering with the tests. In addition, completion of questionnaires relating to mood, behavior and executive function was not possible in respectively nine and sixteen patients due to developmental delay. Twenty-five patients were not able to undertake the full assessment of intelligence due to severe communication difficulties or motor impairment. Total IQ was not significantly correlated with HR-QoL in the remainder thirty-five patients (p=0.364). However, as a potential bias could not be excluded, IQ was excluded from further analyses.

When comparing non-lesional and lesional dystonia, children and young adults with lesional dystonia had more severe symptoms, reflected in higher scores on the BMFDRS (median 89.6 vs 24.6) and GCI-S (median 6.0 vs 4.0) and lower scores on gross motor

functioning (GMFM median 59.1% vs 100.0%) and upper limb functioning (MAULLF median 60.0% vs 87.3%). Moderate or severe pain was less frequently reported in non-lesional dystonia patients (24% vs 42%). Elevated scores on internalizing problems were found in 47% of the non-lesional patients and 35% of the lesional patients.

Principal component analysis

The PCA of the whole group resulted in three principal components (Table 3). The 'motor symptoms' component comprised the BFMDRS, GCI-s, GMFM and MAULLF scores and explained 53% of the variance. The second component was labelled as 'mood and executive function' and the internalizing subscale on the CBCL/ABCL and total BRIEF score (22% of variance). The 'pain' component consisted of the NPRS and accounted for 15% of the variance. The components did not differ for list wise or pair wise deletion of cases (Supplement 1) and showed a sufficient Cronbach's Alpha coefficient.

HR-QoL assessment and it's predictors

Comparing HR-QoL scores between the whole sample with healthy Dutch children (mean age 12.1 SD 3.2, 57% boys), revealed substantially lower scores.[20] This was the case for total HR-QoL (58.6±20.7 vs 87.6±11.0), as well as physical (49.3±19.6 vs 92.2±9.1) and psychosocial domains of functioning (64.0±17.1 vs 88.8±9.7). HR-QoL was not significantly correlated with gender or disease duration and showed a mild correlation with age that disappeared when corrected for extent of motor symptoms (ρ=0.39; p<0.05 and p=0.364 respectively). In addition, age did not significantly correlate with the non-motor outcome measures (p=0.640-p=840).

Bootstrapping of the components showed stable distributions (Supplement 1). For the total sample, HR-QoL was significantly associated with the motor symptoms, mood and executive function and pain (adjusted R^2=0.66, p<0.001) (Table 4). In non-lesional dystonia, HR-QoL was only significantly associated by mood and executive function (adjusted

R^2=0.53, p<0.001). For lesional dystonia, motor functioning and mood and executive function were predictors (adjusted R^2=0.51, p=0.006).

DISCUSSION

In this study, we showed that the HR-QoL is reported to be substantially low for children and young adults with dystonic syndromes. HR-QoL is strongly correlated with motor and non-motor function (mood, executive functioning and pain). Subgroup analysis revealed motor and non-motor influences on HR-QoL in lesional dystonia, whereas mood and executive functioning were the only significant predictors in non-lesional dystonia.

In our sample we found a significantly lower HR-QoL in comparison to healthy Dutch controls that could not be explained solely by the dystonia severity and motor functioning. The possible contribution of non-motor symptoms to HR-QoL in childhood dystonia has been highlighted, but has never been systematically studied before.[22] Still, treatment strategies mainly focus on motor symptoms.[23] Although dystonia severity and motor functioning scales may reflect severity of motor symptoms, these outcome parameters should not be confused with overall wellbeing of patients.

Mood and executive functioning were at least as important as motor symptoms for perceived HR-QoL. We also found a high prevalence of abnormal depression and anxiety scores compared to the general population, suggestive for more frequently present psychiatric problems in childhood-onset dystonia. The significance of behavioral problems is in line with literature in adult dystonia, where the presence of psychiatry co-morbidity is highly associated with a decreased HR-QoL.[6,7] To our knowledge, this is the first systematic report to directly link non-motor symptoms to HR-QoL and thereby underscores the necessity to systematically evaluate non-motor symptoms in young patients with dystonia to capture the true disease burden.

Pain is the most frequently reported concern in childhood dystonia.[24,25] Despite the presence of moderate to severe pain in a third of our sample, pain seemed a less important predictor of HR-QoL. Possibly, the NPRS was not sensitive enough. A recently proposed model for the care of young patients with dystonia highlighted these difficulties, proposing the assessment of the consequences of pain on daily living rather than directly measure the pain in order to capture the perceived impact of pain in this heterogeneous population.[26]

In our study, we found differences between non-lesional and lesional dystonia patients. While non-motor symptoms are important across the whole sample, motor problems were only associated with a lower HR-QoL in lesional dystonia patients. This could be partly explained by more severe motor symptoms in the lesional dystonia subgroup and the power of the study that was based on the total sample. However, 14/29 non-lesional dystonia patients had a generalized dystonia with moderate to severe motor impairments, still not leading to a significant association with HR-QoL. Studies in adults with non-lesional dystonia also have repeatedly shown only fair to absent associations between motor severity and HR-QoL.[6,7] Although motor symptoms seem more important in lesional dystonia, clinicians must be aware of the possible underlying (non-motor) stressors of these symptoms. The frequently overlapping cognitive impairments and/or limited communication abilities in lesional dystonia likely limits their ability to express their concerns.[4] An aggravation of motor symptoms may be the sole indicator for the presence of a physical or mental stressor. Examples include dystonic storms triggered by an ileus or painful dislocated hip.[27,28] As the HR-QoL is not associated with motor symptoms in non-lesional dystonia and only partly in lesional childhood-onset dystonia, physicians should be more cognizant of non-motor aspects.

There are several limitations to our study. Firstly, although we kept the inclusion criteria as wide as possible, we still do not know exactly to what extent our patient sample reflects the population of young patients with childhood-onset dystonic syndromes. We chose to include

children and young adults. In the general population, prevalence of emotional disorders tends to be lower in children.[29] Given our finding that non-motor symptoms are an important determinant of quality of life, it may be queried whether the importance of non-motor symptoms was equal across both age groups. In fact we found no relationship between severity of non-motor symptoms and age, suggesting that non-motor symptoms are important for both children and young adults. Secondly, several of the used outcome measures we used are not validated for the study sample. However, the BFMDRS is commonly used in children and young adults with dystonia. In addition, the GMFM and MAULLF, originally developed for children with CP, have been used in young adults with CP[30] and childhood dystonia.[31] We selected widely used measures to ensure it was the most reliable approach to compare patients across the whole spectrum of dystonic syndromes. The choice of broad outcome measures might have led to overlooked problems in specific areas within these domains. However, our aim was to first highlight the presence and importance of different (non-)motor features and a more detailed description might be an interesting scope for future studies. Lastly, we used questionnaires completed by the patients' caregivers to measure HR-QoL, mood and behavior and executive functioning, and as a consequence sensitive for rater bias. Moreover, there might be a difference in the perception of problems between patients and parents due to a possible impaired self-awareness in patients. However, 33% of the patients were unable to complete questionnaires themselves due to an intellectual disability, communication difficulties and/or age. This led to missing values, but exclusion of these patients would have led to a non-representative subpopulation. Although we are aware of the possible differences in interpretation between parents and patients, this was the most consistent approach to gather information across the whole population.

In conclusion, HR-QoL is low in children and young adults with dystonia. In non-lesional dystonia, this low HR-QoL is influenced by the presence of anxiety and depressive

symptoms and problems in executive functioning, whereas in children and young adults with lesional dystonia motor symptoms play an additional role. These findings support the hypothesis that non-motor symptoms play an important role in the phenotypic characterization of the dystonia disease. We suggest a multidisciplinary approach to young patients with dystonia to assess both motor functioning and non-motor symptoms to optimize management of this patient population.

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CONTRIBUTORS

HE was involved in the design and conceptualization of the study, analysis and interpretation of the data, drafting and revision of the manuscript. MAC, MHE, WSV, AE, RdJ and RT were conceptualized and designed the study, collected data as part of the multidisciplinary team, and reviewed and revised the manuscript. KJP and DAS collected data, and critically reviewed the manuscript. MAT conceptualized and designed the study, coordinated data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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