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Myoclonus-dystonia: Distinctive motor and non-motor phenotype from other dystonia syndromes

Elze R. Timmers[a], Marenka Smit[a], Anouk Kuiper[a], Anna L. Bartels[a,b], Sterre van der Veen[a], A.M. Madelein van der Stouwe[a], Patrick Santens[c], Bruno Bergmans[c,d], Marina A.J. Tijssen[a,*]

[a] Department of Neurology, University Medical Center Groningen, University of Groningen, PO Box 30.001, 9700 RB, Groningen, the Netherlands
[b] Department of Neurology, Ommelander Hospital Group, PO Box 30.000, 9930 RA, Delfzijl, the Netherlands
[c] Department of Neurology, Ghent University Hospital, 9000, Ghent, Belgium
[d] Department of Neurology, A.Z. Sint-Jan Brugge-Oostende AV, 8000, Bruges, Belgium

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ABSTRACT

Background: Myoclonus-dystonia (M-D) due to a pathogenic variant of *SGCE* is an autosomal dominant inherited movement disorder. Apart from motor symptoms, psychiatric disorders are highly prevalent in patients with M-D. Previous studies suggest, but never tested directly, that the type of psychiatric disorder differs between dystonia syndromes, probably related to disease specific pathology. Little is known about other non-motor symptoms (NMS) in M-D. Here, we systematically study NMS in M-D in direct comparison to other types of dystonia and healthy controls.

Methods: Standardized questionnaires were used to assess type and severity of psychiatric co-morbidity, sleep problems, fatigue and quality of life. Results of M-D patients with a pathogenic variant of *SGCE* were compared to results of idiopathic cervical dystonia (CD) patients, dopa-responsive dystonia (DRD) patients with a pathogenic variant of *GCH1* and controls.

Results: We included 164 participants: 41 M-D, 51 CD, 19 DRD patients, 53 controls. Dystonia patients (M-D, CD and DRD) had an increased prevalence of psychiatric disorders compared to controls (56–74% vs. 29%). In M-D we found a significantly increased prevalence of obsessive-compulsive disorder (OCD) and psychosis compared to CD and DRD. All dystonia patients had more sleep problems (49–68% vs. 36%) and fatigue (42–73% vs. 15%) than controls. Compared to other dystonia subtypes, M-D patients reported less excessive daytime sleepiness and fatigue.

Conclusion: Psychiatric comorbidity is frequent in all dystonia types, but OCD and psychosis are more common in M-D patients. Further research is necessary to elucidate underlying pathways.

1. Introduction

Myoclonus-dystonia (M-D) is a rare hyperkinetic movement disorder. About 50% of the patients have a known pathogenic variant in the epsilon-sarcoglycan gene (*SGCE*), which has an autosomal dominant inheritance pattern with maternal imprinting [1]. Symptoms usually start in the first or second decade of life. The typical clinical picture is that of a relatively mild dystonia in the hands (writer's cramp) and neck, and more pronounced myoclonus in the upper body which is alcohol responsive [2].

Apart from the motor symptoms, non-motor symptoms (NMS), especially psychiatric disorders, are highly prevalent in patients with M-D. A large international study and other smaller studies showed a higher incidence of social phobias, alcohol dependence and obsessive compulsive disorder (OCD) in M-D patients [3–5].

In other types of dystonia, both focal and generalized forms, psychiatric features are also common. Previous studies suggest that the type of psychiatric disorder differs between dystonia subtypes: depression is the main psychiatric disorder in early-onset generalized torsion dystonia, X-linked dystonia parkinsonism and dopa-responsive dystonia (DRD); anxiety disorders in focal dystonias; substance abuse and psychotic disorders in rapid-onset dystonia-parkinsonism [6,7]. However, each of these studies focused on one specific type of dystonia, and results are difficult to compare due to differences in methodology.

* Corresponding author. Department of Neurology, University Medical Center Groningen, Hanzeplein 1, 9700RB, Groningen, the Netherlands.
E-mail addresses: e.r.timmers@umcg.nl (E.R. Timmers), m.smit03@umcg.nl (M. Smit), a.kuiper@umcg.nl (A. Kuiper), a.l.bartels@umcg.nl (A.L. Bartels), s.van.der.veen04@umcg.nl (S. van der Veen), a.m.m.van.der.stouwe@umcg.nl (A.M.M. van der Stouwe), patrick.santens@ugent.be (P. Santens), bruno.bergmans@azsintjan.be (B. Bergmans), m.a.j.de.koning-tijssen@umcg.nl (M.A.J. Tijssen).

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In addition to the psychiatric disorders, other NMS that are prevalent in dystonia are sensory abnormalities, pain, sleep disorders, a high level of fatigue and cognitive problems. In general, patients with dystonia have a higher frequency of all these NMS, but there are no studies focusing on non-psychiatric NMS in M-D patients. It is important to note that NMS have a considerable influence on the quality of life (QoL) of dystonia patients [8]. Some studies show that NMS have a larger impact on the QoL than the motor symptoms, highlighting the burden of NMS.

Nowadays, the NMS are considered to be part of dystonia phenotypes rather than secondary to the social effect of living with a chronic movement disorder. The high prevalence of NMS in dystonia patients before the onset of motor symptoms supports this hypothesis [7]. Furthermore, lack of association between the severity of the psychiatric symptoms and the severity of motor symptoms in both cervical dystonia and generalized dystonia decreases the likelihood that NMS are a secondary effect of the motor symptoms [9,10]. If NMS are part of the phenotype and therefore share a pathophysiological pathway with the motor symptoms, we hypothesize that specific types of dystonia are associated with specific NMS.

In this report, we performed a systematic assessment of psychiatric features, sleep disorders and fatigue in M-D and compared these to a group of normal controls without dystonia and two other types of dystonia that are of special interest: idiopathic cervical dystonia (CD) and DRD. Dystonia of the neck is one of the predominant features of M-D. Although the age of onset in CD is later, the social impact and visibility for the environment are similar. DRD is a group of inherited disorders due to a defect in the synthesis of dopamine. In this study we chose to include only the most common DRD type which is caused by an autosomal dominant inherited pathogenic variant in the *GCH1* gene. Although not entirely correct, this form of DRD will be referred to as DRD in the rest of this article. It is suggested that NMS are part of the phenotype in DRD. The similar age of onset and comparable severity of symptoms, which usually do not lead to loss of independence, make DRD patients a suitable control group.

Establishing which NMS are most prevalent in different dystonia syndromes may shed light on the pathophysiology of the NMS. Furthermore, more insight in NMS in different types of dystonia allows for better personalized treatment and thereby improvement of QoL for dystonia patients.

2. Methods

2.1. Study population

M-D patients with a confirmed pathogenic variant in the *SGCE* gene were included. Data of three control groups were used: 1) clinically confirmed isolated CD patients, 2) DRD patients with a confirmed pathogenic variant in the *GCH1* gene, 3) controls without a movement disorder (results were previously reported [8,9,11]). All participants were adults (age ≥ 18 years). Exclusion criteria were the presence of other neurological conditions or treatment with deep brain stimulation. In addition, healthy participants with relatives with dystonia and, due to exclusion criteria of the previous study [8,11], CD patients using antidepressant treatment were excluded. Patients were recruited in several Dutch hospitals and via the dystonia patient association, some M-D patients were also recruited from Belgium. Controls were acquaintances of patients or investigators or were recruited by advertisements. Informed consent was obtained from all participants and the study was approved by the medical ethics committee of the University Medical Center Groningen (METc 2014/034).

2.2. Clinical characteristics, NMS and QoL

Clinical and demographic characteristics of the patients were obtained by a standardized interview. Information about the duration of dystonia and medication regimen were recorded. A standardized videotaped examination was performed in all patients. The severity of the motor symptoms was scored by two independent experts. The 7-point Clinical Global Impression Scale (CGI-S) was used to score motor severity in all patients [12]. In M-D, severity of dystonia was assessed with the Burke Fahn Marsden Dystonia Rating Scale (BFMDRS) [13], and severity of myoclonus with an abbreviated version of the Unified Myoclonus Rating Scale (UMRS) [14]. In the CD group the severity of the torticollis was assessed with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [15]. In the DRD group the BFMDRS was used to assess severity of dystonia. The presence of psychiatric disorders, including substance and alcohol abuse, as defined in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV), was evaluated with the Mini International Neuropsychiatric Interview – PLUS (MINI-PLUS) [16]. The severity of current depressive, anxious and obsessive compulsive symptoms were assessed with respectively the Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI) and the Yale Brown Obsessive Compulsive Scale (YBOCS) [17–19]. Impaired sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI), excessive daytime sleepiness with the Epworth Sleepiness Scale (ESS) and fatigue was assessed with the Fatigue Severity Scale (FSS) [20–22]. The RAND-36 item Health Survey (RAND-36) was used to assess the QoL [23]. More information and cut-off values of the questionnaires can be found in Supplementary Table 1.

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 23. A p-value < 0.05 was considered statistically significant. All baseline data were quantitatively described. A pairwise deletion of missing data was used.

Fisher-Freeman-Halton exact tests were performed to compare the presence of a DSM-IV diagnosis between respectively all groups and the three patient groups. For variables which showed a significant difference between the patient groups post hoc analysis were performed using a Bonferroni corrected p-value.

One way ANOVA, or in case of non-normality Kruskal Wallis test, was performed to compare the psychiatric, sleep and QoL scales between all groups and the three patient groups. Post-hoc analysis with Bonferroni correction of the p-values was performed for the variables which showed a significant difference. The scores on the domains of the RAND36 were combined into a mental health component and a physical health component using factor analysis as described previously.

We performed a correlation analysis to assess the association of age of onset with the presence of psychiatric co-morbidity. Next, logistic regression was performed on the variables with a p-value of < 0.05 in the correlation analysis. Odds ratios with and without age at onset as covariate were compared. To assess the influence of motor symptoms on having a psychiatric disorder a binary logistic regression analysis was performed.

Associations between QoL and clinical characteristics were assessed using correlation analysis. With multivariate regression analysis, we determined the influence of the variables with a $p < 0.05$ in the univariate correlation analysis. Assumptions of normality, multicollinearity and homoscedasticity of the multivariate regression analysis were checked.

3. Results

We included 164 participants: 41 M-D patients, 51 CD patients, 19 DRD patients, and 53 controls. The mean age was 49 years (range 22–75 years) in M-D patients, 54 years (range 20–80) in CD patients, 51 years (range 22–77) in DRD patients, and 53 years (range 20–83) in controls. No significant differences in age and gender were found between groups. Age of onset was significantly higher in CD patients (43 years, range 18–70) than in M-D patients (6 years, range 0–50) and

Table 1
Clinical characteristics of participants.

	M-D n = 41	CD n = 51	DRD n = 19	p-value	Controls n = 53	p-value
Age	48.7 (15.7)	54.2 (10.6)	51.1 (15.6)	0.148	53.4 (12.9)	0.204
Gender M/F	20/21	15/36	5/14	0.098	16/37	0.151
Age of onset	5.5 (0–60)	43 (18–70)	7 (1–20)	0.000**		
Disease duration	45 (7–73)	10 (1–52)	40 (18–71)	0.000**		
Video rating						
BFMDRS	5.4 (5.2)		6.9 (5.4)			
UMRS	13.8 (16.5)					
TWSTRS		14.1 (4.8)				
CGI-S	2.1 (1.3)	3.9 (1.4)	1.9 (0.6)			

One way anova, kruskal wallis test and fisher-freeman-halton exact test were performed to compare the three patient groups and all four groups. BFMDRS:Burke Fahn Marsden Dystonia Rating Scale; UMRS:Unified Myoclonus Rating Scale; TWSTRS:Toronto Western Spasmodic Torticollis Rating Scale; CGI-S: Clinical Global Impression Scale M-D:myoclonus-dystonia; CD:cervical dystonia; DRD:dopa-responsive dystonia., **p < 0.01.

DRD patients (7 years, range 1–20). Clinical characteristics are described in Table 1.

Nine patients with M-D were treated with medication, most often with clonazepam (n = 6), but also treatment with levetiracetam (n = 2), trihexyphenidyl or valproate acid (both n = 1) was reported. Almost all CD patients (n = 47) received botulinum toxin injections and most DRD patients (n = 17) were on levodopa treatment. Six M-D patients received antidepressant treatment with paroxetine (n = 3), venlafaxine (n = 2) or escitalopram (n = 1). None of the CD patients and controls received treatment with antidepressants. Three DRD patients were on treatment with either mirtazapine (n = 2) or paroxetine (n = 1).

3.1. Psychiatry

Dystonia patients had visited their family doctor or mental health care professional due to mental problems significantly more often compared to controls (dystonia patients 65% (M-D = 68%, CD = 65%, DRD = 58%) vs. controls 35%; p = 0.01). Accordingly, 56% of the M-D patients met the criteria of any psychiatric disorder according to the DSM-IV at any point in their lives, which was comparable to the prevalence in CD (65%) and DRD (74%) patients versus a prevalence of 29% in the controls (p < 0.01) (Table 2).

The prevalence of almost all studied DSM-IV diagnoses were significantly different between the four groups (Table 2). When the results of M-D patients were compared to the other two dystonia groups, a significant difference was found in the presence of obsessive compulsive disorder (OCD) (M-D = 20%, CD = 2% and DRD = 11%, p = 0.01), generalized anxiety (M-D = 5%, CD = 12% and DRD = 47%, p = 0.00), and psychosis (M-D = 10%, CD = 0% and DRD = 0%, p = 0.03). Post hoc analysis showed significantly more OCD in M-D patients compared to CD patients (p = 0.03). Moreover, there was a higher prevalence of generalized anxiety in the DRD group compared to the M-D (p = 0.00) and CD patients (p = 0.01).

To rule out any biases due to age at onset, we performed a correlation analysis to assess the association of this variable with the presence of psychiatric co-morbidity (Supplementary Table 2). Next, logistic regression was performed on the variables with a p-value of < 0.05 in the correlation analysis. Odds ratios with and without age at onset as covariate were compared. Results show that the age of onset of motor symptoms had an influence on the odds ratio of panic disorder and OCD between CD and DRD, and CD and M-D patients, meaning that age of onset might have some influence on our significant finding of more OCD in the M-D group (odds ratio: 0.083, p = 0.02 vs. odds ratio with age of onset as covariate: 0.218, p = 0.40) (Supplementary Table 3). We assessed whether motor symptom characteristics (severity, duration of dystonia, age of diagnosis, or duration of levodopa treatment) predict the presence of a psychiatric disorder. We found no significant association between motor characteristics and presence of a psychiatric disorder (Supplementary Table 4).

Scores reflecting the severity of depression and anxiety were statistically different between the four groups (both p < 0.01), but were not significantly different between the patient groups (p = 0.07 and p = 0.27) (Table 3). No differences were found in the scores concerning severity of OCD.

3.2. Sleep and fatigue

In M-D, almost half of the patients subjectively reported to have sleep problems (49%) and in CD and DRD sleep problems were even more common (resp. 61% and 68%). This was significantly different compared to controls (36%, p = 0.04). A large proportion (42%) of the M-D patients, 73% of the CD and 58% of the DRD patients reported that they were more easily fatigued than their peers. This is a significantly

Table 2
Prevalence of psychiatric diagnoses according to the DSM IV assessed using the MINI PLUS.

	M-D n = 41	*CD n = 51*	*DRD n = 19*	p-value	*Controls n = 51*	p-value
Any psychiatric disorder	23 (56%)	33 (65%)	14 (74%)	0.411	15 (29%)	0.001**
Depressive disorder	15 (37%)	16 (31%)	8 (42%)	0.673	7 (14%)	0.024*
Generalized anxiety	2 (5%)	6 (12%)	9 (47%)	0.000**	0 (0%)	0.000**
Panic disorder	13 (32%)	6 (12%)	4 (21%)	0.061	1 (2%)	0.000**
Agoraphobia	12 (29%)	12 (24%)	8 (42%)	0.309	1 (2%)	0.000**
Social phobia	5 (12%)	9 (18%)	4 (21%)	0.579	0 (0%)	0.003**
Specific phobia	7 (17%)	8 (16%)	3 (16%)	1.000	2 (4%)	0.122
OCD	8 (20%)	1 (2%)	2 (11%)	0.014*	0 (0%)	0.000**
Psychosis	4 (10%)	0 (0%)	0 (0%)	0.032*	0 (0%)	0.009**
Dysthymia	1 (2%)	4 (8%)	1 (5%)	0.554	0 (0%)	0.144
Hypomania	4 (10%)	2 (4%)	2 (11%)	0.432	0 (0%)	0.056
Alcohol dependence	3 (7%)	2 (4%)	1 (5%)	0.857	3 (6%)	0.960

Values are presented as number (percentage%). Fisher-Freeman-Halton exact tests were performed to compare the three patient groups and all four groups. OCD:obsessive compulsive disorder; M-D:myoclonus-dystonia; CD:cervical dystonia; DRD:dopa-responsive dystonia. *p < 0.05, **p < 0.01.

Table 3
Severity of psychiatric symptoms and sleep and fatigue.

	M-D	CD	DRD	*p-value*	Controls	p-value
Psychiatry	*N = 40*	*N = 51*	*N = 18*		*N = 53*	
BDI	7.5 (0–30)	8.0 (0–28)	5.0 (0–18)	0.067	2.5 (0–19)	0.000**
BAI	7.5 (0–42)	8.0 (1–31)	6.0 (0–31)	0.267	3.0 (0–21)	0.000**
YBOCS	0.0 (0–12)	0.0 (0–12)	0.0 (0–18)	0.917	0.0 (0–2)	0.074
Sleep	*N = 40*	*N = 44*	*N = 19*		*N = 46*	
ESS (SD)	7.3 (5.5)	8.8 (6.9)	12.1 (6.4)	0.030*	5.8 (4.9)	0.003**
FSS (SD)	35.0 (15.7)	39.6 (15.7)	36.9 (18.1)	0.425	24.0 (12.4)	0.000**
PSQI (SD)	5.9 (3.2)	7.4 (3.9)	8.9 (4.7)	0.016*	5.2 (4.3)	0.001**
Quality of Life	*N = 41*	*N = 51*	*N = 19*		*N = 52*	
QoL PC	50.0 (22–65)	44.3 (21–62)	49.0 (27–63)	0.010**	53.8 (26–62)	0.000**
QoL MC	46.8 (10–64)	48.4 (25–59)	50.0 (14–59)	0.520	55.5 (36–62)	0.000**

Values are presented as median (range) or as mean (SD) (as indicated). Kruskal wallis test or one way anova were performed to compare the three patient groups and all four groups. BDI: Beck Depression Inventory; BAI:Beck Anxiety Inventory; YBOCS:Yale Brown Obsessive Compulsive Scale; ESS:Epworth Sleepiness Scale; FSS:Fatigue Severity Scale; PSQI:Pittsburg Sleep Quality Index; QoL PC:physical component of quality of life; QoL MC:mental component of quality of life; M-D:myoclonus dystonia; CD:cervical dystonia; DRD:dopa-responsive dystonia. *p < 0.05, **p < 0.01.

higher percentage than in the controls (15%, p = 0.00).

The scores on all questionnaires about sleep disturbances and fatigue were higher in the dystonia group compared controls (Table 3). Moreover, the scores reflecting excessive daytime sleepiness (ESS) and quality of sleep (PSQI) differed significantly between patient groups. Post hoc analysis showed significantly more excessive daytime sleepiness and a worse quality of sleep in DRD compared to M-D patients (p = 0.03 and p = 0.02).

In M-D, mean scores on the questionnaires concerning sleep and fatigue were not, or only marginally, above the clinical cut-off value (ESS = 7.3, cut-off = 10; PSQI = 5.9, cut-off = 5; FSS = 35, cut-off = 36) and only the score indicating fatigue was significantly higher compared to controls (p = 0.00).

3.3. Quality of life

The scores on the questionnaire concerning QoL differed between the four groups (see Table 3). Post hoc analysis showed a difference between M-D and CD patients (p = 0.01), with a higher perceived physical QoL for the M-D patients (score of 50 vs. 44).

Univariate analysis of the whole dystonia group showed a negative association between the QoL and almost all NMS (Supplementary Table 5). Multivariate analysis in the whole dystonia group showed that more fatigue (FSS) was associated with a lower physical QoL (β: -0.23, p = 0.00, Supplementary Table 6). More depressive and anxious symptoms were associated with a lower mental QoL (β: -0.49, p = 0.00; β: -0.42, p = 0.00).

4. Discussion

To the best of our knowledge, this is the first study reporting on the prevalence of NMS in M-D in direct comparison to other dystonia subtypes. We found a high prevalence of psychiatric disorders in all types of dystonia with more OCD and psychosis in M-D compared to CD and DRD patients. Further, dystonia patients had more sleep problems and fatigue than healthy controls. Compared to other dystonia subtypes, M-D patients reported less excessive daytime sleepiness and fatigue. QoL was lower in the dystonia groups compared to controls and associated with NMS, showing that NMS are an important burden for the dystonia patients.

Psychiatric co-morbidity was highly prevalent in the M-D group with depressive disorder (36%), panic disorder (31%), agoraphobia (28%) and OCD (19%) being most common. Previous studies reported a comparable prevalence of these psychiatric disorders [3,5]. Conversely, compared to previous studies we found a low rate (7%) of alcohol dependence in our cohort [4,5]. We do not have a clear explanation for this finding, perhaps this is due to a greater awareness of the risks of alcohol dependence in M-D, or underreporting due to shameful feelings.

Compared to DRD and CD patients, in M-D patients we saw a higher incidence of OCD and psychosis. Four M-D patients experienced some features of psychosis (including auditory and/or visual hallucinations and/or persecutory delusions) at some point in their lives. This relatively high prevalence of psychosis in our cohort (10%) has only been reported before in two M-D families [24,25]. Alterations of the dopaminergic signaling in the striatum are hypothesized to play a role in developing psychosis, especially an imbalance between D2 and D1 receptors have been reported and blockage of D2 receptors with antipsychotic treatment is in some cases successful [26]. In M-D the dopaminergic signaling in the striatum also plays a role, however, in a *SGCE* knock out mouse model and in M-D patients a reduced radiotracer uptake of striatal D2 receptors was found [27]. Alterations in the dopaminergic system are part of the pathophysiology of both psychosis and M-D. This suggests that psychosis might be part of the phenotype of M-D, however the underlying mechanisms need further study.

The relatively high prevalence of OCD in M-D is of special interest because OCD is not considered to be a consequence of living with a chronic disease. Although the precise pathophysiological pathways of both M-D and OCD are not fully known, some similarities have been suggested. Dysfunction of cortico-striatal connections is hypothesized to be responsible for OCD [28], and an altered long-term depression of the cortico-striatal synapses was found in a mouse model with a decreased expression of *SGCE*, representing M-D [2]. The globus pallidus interna (GPi) is another structure of interest and plays a role in both the pathophysiology of OCD and M-D. Successful deep brain stimulation (DBS) of the GPi in patients with Tourette syndrome and OCD has been described [29]. Similarly, GPi DBS has proven to be a successful treatment in M-D and a previous study showed abnormal neuronal activity in the GPi of M-D patients compared to other dystonias [30]. Another clue that OCD and M-D share a common pathway is the role of mono-amine neurotransmitters, especially serotonin: in M-D, lower levels of serotonin metabolites in CSF have been reported [31]. In OCD, the serotonergic metabolism also plays a role, with selective serotonin reuptake inhibitors being the first and most effective pharmacological treatment option. The shared dysfunction in brain networks and the mono-amine neurotransmitters dopamine and serotonin are highly suggestive that NMS and motor symptoms in M-D have a common pathophysiological pathway.

In our study we found an increased prevalence of anxiety disorders in all dystonia patients compared to controls. The prevalence of generalized anxiety (47%) in the DRD group was even higher than in M-D and CD patients. The serotonergic metabolism is also hypothesized to play a role in both DRD and generalized anxiety. The impaired synthesis of tetrahydrobiopterin in DRD leads to an impaired synthesis of other mono amines such as serotonin [32]. In generalized anxiety,

disruption of the serotonergic system, especially the pathway leading from the dorsal raphe nucleus via the amygdala to the frontal cortex, is known to play a role [33]. Although DRD was not the primary focus of our study, this further supports our hypothesis of a motor phenotype specific psychiatric phenotype with different, dystonia-syndrome-specific pathophysiological pathways at play.

Apart from the psychiatric disorders, we found more fatigue in the M-D group compared to controls, however, fatigue scores in the M-D group were lower compared to the DRD patients. This might be due to the dopaminergic medication but could also be explained by changes of neurotransmitters in the basal ganglia, including serotonin and dopamine which are suggested in fatigue [34]. Pathogenic variants in the *SGCE* gene (M-D) and *GCH1* gene (DRD) might influence these neurotransmitter pathways in a different way, leading to dystonia-specific NMS.

Our study has some limitations: first, the sample sizes of our groups were unequal. This unbalanced design was due to the rare nature of especially DRD. Furthermore, the age of onset of the dystonia subtypes was different in our cohort. Our analysis showed that age of onset influenced the odds ratio of OCD in M-D compared to CD patients. This might have had some influence on our finding of significantly more OCD in the M-D versus the CD patients. However, DRD patients have a similar age of onset as M-D patients but have a prevalence of OCD that is almost half the prevalence in M-D patients (11% vs. 20%). Another limitation of this study is the lack of antidepressant treatment in the CD group due to inclusion criteria of the previous study, which might have underestimated the rate of psychiatric disorders in this group. Eight CD patients were not included because they were using various antidepressants; and several additional patients were not asked to participate because of known medication use. The questionnaires about sleep disorders and fatigue were not validated for use in dystonia patients. However, they are widely used and the ESS and FSS are shown to have good psychometric properties in dystonia patients [35,36]. In this study, some NMS, including pain and cognitive problems, were not assessed. Further studies are recommended to characterize these symptoms in dystonia patients.

In conclusion, dystonia patients have a high incidence of NMS, especially psychiatric features, sleep problems and fatigue, compared to controls. More specifically, in M-D patients the prevalence of OCD and psychosis is increased compared to CD and DRD patients, suggesting a disease specific motor and non-motor phenotype. This is further supported by the relatively increased incidence of generalized anxiety in DRD patients.

Further research is necessary to elucidate the underlying pathways, with special attention for the involvement of neurotransmitters. Clinicians should be aware of the psychiatric co-morbidity, sleep disturbances and fatigue in dystonia in general, with a special focus on OCD in M-D. The major influence of NMS on the QoL shows that NMS are an important burden for dystonia patients and highlights the necessity of early recognition and treatment of the NMS. An increased awareness for and personalized and adequate treatment of NMS might lead to an improved QoL of the patients.

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Data statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Authors' roles

ERT, MS, AK, ALB and MAJT contributed to the conception and organization of the research project. ERT, MS, AK, ALB, SV, AMMS, BAB and PS collected the data. ERT designed and executed the statistical analysis, MS and MAJT reviewed the analysis. ERT, MS and MAJT wrote the first draft of the article, all authors reviewed and edited the final manuscript.

Declaration of competing interest

None.

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Appendix A. Supplementary data

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