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Cognition in children and young adults with myoclonus dystonia – A case control study

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ABSTRACT

Introduction: In adult patients with myoclonus dystonia (MD), cognitive deficits regarding information processing speed and executive functioning have been demonstrated, but it is unclear whether cognition is also affected in young MD patients. The present study investigates cognition in young MD patients and the role of an SGCE mutation.

Methods: In this case control study 20 young MD patients (9 children (5.75–12.58 years) and 11 adolescents/young adults (13.5–25.42 years)) were included and compared to an age-, IQ- and gender-matched healthy control group (n = 40). Within the patient group, we compared patients with (n = 12) and without (n = 8) an SGCE mutation (SGCE+/-). All participants completed neuropsychological tests for memory, attention/processing speed, executive functioning, social cognition and language.

Results: Overall, patients performed in the (low) average range, comparable to healthy controls. Only on a semantic fluency test, patients scored significantly lower. SGCE+ patients had lower emotion recognition scores (a social cognition test) compared to SGCE-patients.

Conclusion: We could not demonstrate cognitive deficits as found in adult MD patients in our younger group. Patients performed on the same level as healthy controls, with only a small difference in semantic fluency. We did not find executive deficits that were manifest in adult SGCE+ patients, but we did find an association of an SGCE mutation and lower scores on a social cognition test. Similar to executive functioning, social cognition is a prefrontally regulated function, but had not been tested in adult MD. Hence, social cognition may precede executive problems in adulthood, suggesting growing into deficit.

1. Introduction

Myoclonus Dystonia (MD) is a form of Early Onset Dystonia (EOD), a rare disabling neurological movement disorder manifesting before the age of 26 years. Albanese et al. [1] described dystonia as “sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both”. MD is characterized by myoclonus of the upper limbs and often task-specific dystonia, such as writer’s cramp. It is associated with a mutation in the ε-sarcoglycan gene (SGCE) in about 50 % of cases (SGCE+). The other 50 % are idiopathic cases of MD (SGCE-).

Most studies have focused on the motor symptoms, but non-motor symptoms, including cognitive deficits increasingly gain interest. Dystonia is thought to involve the loss of inhibition, sensory dysfunction and abnormal plasticity [2] of the neural circuitry in which the basal ganglia, the cerebellum and the prefrontal cortex take part [3]. This brain network also plays an important role in the regulation of cognitive functions [4,5]. Hence, cognitive deficits concerning attention and processing speed, and in particular prefrontally regulated higher order cognitive functions such as executive functions and social cognition, can be expected in dystonia patients.

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Deficits in these cognitive functions have indeed been found in adult MD patients [6,7]. Van Tricht et al. [6] showed that adult (mean age 45.9 years) *SGCE* + patients have executive problems and deficits on a semantic fluency task compared to healthy controls. Adult *SGCE*-patients (mean age 40.0 years), only obtained lower scores on a semantic fluency task. However, in the study by van Tricht et al. social cognition was not evaluated. To date, it is unknown whether such cognitive impairments are also manifest in young patients with MD, and are related to the *SGCE* mutation. To the best of our knowledge, there is only one case report on cognitive functioning in a pediatric MD patient in the literature, a 17-year old girl with borderline IQ scores [8].

Summarizing, we can conclude that the existing literature suggests cognitive deficits, in particular in higher order frontal functions, in adult MD patients with different patterns for *SGCE* + and *SGCE*-patients, but it is unknown whether these cognitive deficits exist already in young MD patients. This is relevant as cognitive deficits may negatively affect participation in school, leisure activities and peer relationships, requiring timely counseling or treatment. With the present case-control study we aimed to investigate whether young patients with MD have cognitive deficits compared to healthy controls, and in particular focus on the presence of impairments in higher order functions such as executive function and social cognition. In addition, we study differences between *SGCE* + and *SGCE*-patients.

2. Method

2.1. Participants

Our sample was drawn from a cohort of 60 EOD patients who visited our neurology outpatient clinic. Inclusion criteria for the patient group were (1) diagnosis of MD made by movement disorders specialists and geneticists (2) age between 5 and 26 years at time of measurement (3) sufficient communicative- and motor skills to complete a neuropsychological assessment. Our sample consisted of two age groups: children (in primary school; 5–12 years) and adolescents/young adults (in secondary school or working; 13–26 years). We compared data of MD *SGCE* + and *SGCE*-patients. Patient data were compared to a 1:2 age-verbal IQ- and gender matched healthy control group, found through convenience sampling in the authors' social networks.

2.2. Material

Severity of motor impairment was assessed with the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS [9]). Scores range from 0 to 120 (highest severity).

Neuropsychological tests

Verbal intelligence was estimated through the Vocabulary and Similarities subtests of the Wechsler Intelligence Scale for Children (WISC-III-NL [10]). For patients of 16 years and older, similar subtests from the WAIS-III-NL [11] were used.

Working memory was tested with the Digit Span subtest of either the WISC-III-NL or WAIS-III-NL. Resulting normscores range from 1 to 20, with a mean of 10 ($sd = 3$).

Verbal learning and verbal memory were assessed with the Dutch version of the Rey Auditory Verbal Learning Task (RAVLT [12]). This test yields two scores, namely RAVLT-IR (immediate recall: verbal learning) and RAVLT-DR (delayed recall: verbal memory). For patients up to 12 years of age, the test results in decile scores and for older patients, the test results in *T*-scores. To facilitate the analysis, scores of all participants were manually transformed into *z*-scores by using the formula: $z = \frac{x-m}{s}$.

Attention/processing speed was tested with the intermediate version of the Trail Making Test part A (TMT-A [13]) and for patients of 18 years and older the full version was used. Time in seconds to complete the test is measured. For patients of 18 years and older, *T*-scores are available.

Table 1

Demographic characteristics of the sample.

	Healthy control group	MD	SGCE+	SGCE-
	N = 40	N = 20	N = 12	N = 8
<i>M</i> _{Age} (<i>SD</i>)	13.27 (4.39)	13.00 (5.03)	11.99 (6.12)	14.52 (2.35)
Age range	6.08–22.80	5.75–25.42	5.75–25.42	10.50–17.58
<i>M</i> _{IQ} (<i>SD</i>)	105.63 (12.34)	99.25	98.83	99.88
		(14.91)	(17.31)	(11.47)
IQ range	85–130	79–145	79–145	81–112
<i>M</i> _{BFMDRS} (<i>SD</i>)	n.a.	16.17	15.64	16.96
		(11.55)	(12.40)	(10.93)
Male/female	21/19	14/6	8/4	6/2

For patients younger than 18 years raw scores are compared to norm group means and standard deviations. All scores were transformed into *z*-scores.

Executive functioning was measured as planning, covered by the subtest Zoo Map of either the Behavioural Assessment of the Dysexecutive Syndrome for Children (BADS-c [14]) or the BADS [15] for patients of 16 years and older. We used the raw score of both conditions of this test for our analysis (Zoo map 1 and Zoo map 2). The maximum (best) score is 8.

Social cognition was measured as emotion recognition with the shortened version (36 items) of the Dutch Facial Expressions of Emotions: Stimuli and Test (FEEST-36 [16,17]). We used the total score of correctly identified pictures (FEEST total), ranging from 0 to 36.

Language was measured with the subtest Word Generation of the NEPSY-II-NL [18] and the semantic Fluency subtest of the Groninger Intelligence Test (GIT-2 [19]) for patients of 18 years and older. Both tests involve naming as many animals as possible within 1 min (Semantic Fluency) and research has shown that tasks like these are also related to cognitive speed [20]. To enable analysis of scores of all patients together, we used *z*-scores of this task.

2.3. Procedure and statistical analysis

The neuropsychological assessment took about 2 h for patients and 1.5 h for healthy controls. The difference in time is the result of patients needing more breaks.

Dependent variables were test scores and the independent variable was Group. For differences between (sub)groups on normally distributed variables, we performed independent sample *t*-tests. Mann-Whitney *U* tests were used for non-normally distributed variables. In case age or BFMDRS scores were significantly correlated with dependent variables, ANCOVA was performed. We applied a significance level of $\alpha = 0.05$ or an adjusted significance level (Bonferroni-Holm) in case of multiple comparisons within a cognitive domain. Cohen's *d* is reported as effect size and classified as $d = 0.2$ as small, $d = 0.5$ as moderate and $d = 0.8$ as large [21]. For non-normally distributed variables, a product moment correlation coefficient ($r = z/(\sqrt{N})$) as described by Rosenthal [22] is used and converted into Cohen's *d*. Missing values were addressed by casewise deletion.

Data were collected between 2013 and 2018 in regular patient care at the University Medical Center Groningen (UMCG). All data were processed anonymously according to GCP. All participants and/or parents gave written informed consent. The Medical Research Ethics Committee (MREC) of the UMCG reviewed the study and declared that the Medical Research Involving Human Subjects Act (WMO; MREC number 2013/012) does not apply.

Fig. 1. Graphical overview over subgroups.

Table 2

Descriptive statistics (M (SD)) and statistical test results for differences on neuropsychological tests for patients and healthy controls.

	Healthy controls N = 40	Patients N = 20	p	Effect size Cohen's d
Verbal IQ	105.63 (12.34)	99.25 (14.91)	.084 ^a	0.482
Digit Span	11.10 (2.91)	10.05 (3.28)	.212 ^a	0.346
RAVLT-IR	-.04 (1.40)	0.04 (1.36)	.824 ^a	0.061
RAVLT-DR	-.31 (1.33)	-.19 (1.32)	.748 ^a	0.088
TMT-A	-.018 (1.60)	0.09 (1.32)	.525 ^a	0.175
FEEST total	27.03 (3.97)	27.00 (4.44)	.943 ^b	0.000
Semantic Fluency	.84 (1.16)	0.07 (1.35)	.025 ^a *	0.631
Zoo map 1	4.88 (3.99)	4.82 (3.23)	.566 ^c	0.144
Zoo map 2	7.70 (0.94)	7.71 (0.99)	.939 ^c	0.012

*significant difference.

^a Based on independent samples *t*-test.

^b based on ANCOVA.

^c based on Mann-Whitney *U* test.

3. Results

3.1. General results

Our sample consisted of 20 patients: 9 children (age range 5–12) and 11 adolescents/young adults (age range 13–26; Table 1). Fig. 1 provides an overview of the different subgroups. There were 12 patients with *SGCE* + (7 children, 5 adolescents/young adults) and 8 *SGCE*- (2 children, 6 adolescents/young adults). Patient data were compared to age- and gender matched healthy controls (n = 40). Descriptive statistics and results of statistical testing can be found in Table 2. Most scores lie in the (below) average range.

3.2. Relation between dystonia severity, age and scores on neuropsychological tests

BFMDRS scores did not correlate significantly with any of the neuropsychological tests. Age correlated significantly with FEEST total ($r = -0.54$, $p = .014$) and was included as covariate in the analyses of FEEST total scores.

3.3. Comparison between patients and healthy controls

Table 2 shows the test scores of patients and healthy controls. Patients had lower scores on the semantic fluency test compared to healthy controls, but the effect was small. On other neuropsychological tests, patients performed on the same level as healthy controls.

Table 3

Descriptive statistics (M (SD)) and test results of neuropsychological tests for *SGCE* + and *SGCE*-patients.

	MD <i>SGCE</i> + and <i>SGCE</i> - patients		p	Effect size Cohen's d
	<i>SGCE</i> + N = 12	<i>SGCE</i> - N = 8		
Verbal IQ	98.83 (17.31)	99.88 (11.47)	.883 ^a	0.068
Digit Span	9.83 (3.43)	10.38 (3.25)	.728 ^a	0.161
RAVLT-IR	-.35 (1.40)	0.62 (1.14)	.120 ^a	0.745
RAVLT-DR	-.43 (1.46)	0.17 (1.06)	.329 ^a	0.458
TMT-A	0.49 (1.44)	-.52 (0.87)	.093 ^a	0.811
FEEST total	25.08 (4.19)	29.87 (3.18)	.030 ^{a, b}	1.152
Semantic Fluency	0.11 (1.34)	0.00 (1.45)	.868 ^a	0.077
Zoo map 1	4.33 (3.08)	5.38 (3.50)	.606 ^c	0.259
Zoo map 2	7.89 (0.34)	7.50 (1.41)	.963 ^c	0.047

*significant difference.

^a Based on independent samples *t*-test.

^b based on ANCOVA.

^c based on Mann-Whitney *U* test.

3.4. Myoclonus dystonia with and without *SGCE* mutation (*SGCE* + and *SGCE*-)

Table 3 provides descriptive statistics of the two MD subgroups and shows that *SGCE* + patients performed worse on the FEEST than *SGCE*-patients even after correcting for age. The effect size indicated a large effect after correcting for age. Other comparisons did not show significant differences.

4. Discussion

In the present case-control study we investigated cognitive functioning in 20 MD patients (9 children and 11 adolescents/young adults) focusing on differences between patients and healthy controls and between *SGCE* + patients and *SGCE*-patients. We focused mainly on prefrontally regulated functions, of which social cognition has not been systematically investigated earlier in this group. Overall, we did not find evidence for substantial differences as patients and controls performed on the same level on almost all neuropsychological tests. The only difference we found was that patients were slower in naming animals on the semantic fluency test. Furthermore, MD *SGCE* + patients had lower emotion recognition scores, a social cognition test, compared to *SGCE*-patients.

In our pediatric and adolescent *SGCE* group we detected significantly lower scores on semantic fluency. Van Tricht et al. [6] found the same difference for adult MD patients (*SGCE* + and *SGCE*-) compared to

healthy controls. We replicated this finding for young MD patients, but also found that the effect size of this difference is small. Therefore, the clinical relevance of this result is probably limited.

For adult *SGCE* + patients, van Tricht et al. found executive dysfunction. We did not find deficits in this domain for our young MD group as a whole, nor for the *SGCE* + group in particular. The lack of executive dysfunction may be related to the concept of growing into deficit, i.e. that executive dysfunction only becomes apparent later in life when these functions are expected to be fully operational.

We did however find a significant lower score in another prefrontally regulated cognitive domain, namely social cognition and in particular emotion recognition. Very few studies have systematically investigated social cognition in young dystonia patients and no results have been published on this domain in MD patients. We found that MD *SGCE* + patients performed significantly worse on a test for emotion recognition than *SGCE*-patients. This fits the existing evidence for deficits in higher order, mostly prefrontally regulated cognitive functions, such as executive functioning.

Deficits in social cognition can impair peer interactions, development of adequate social skills and psychiatric health [23,24]. In MD, the psychiatric comorbidities (obsessive-compulsive disorder and psychosis) are hypothesized to be related to lower levels of serotonin [25,26]. Serotonin has also been linked to social cognition [27], which makes this a probable explanation for our finding. It is possible that social cognition problems can be detected earlier than executive functioning problems as intact social cognition is relevant from a very early age onward [28]. Emotion recognition, as part of social cognition, has been shown to be an important early marker of developing social skills [29].

Our study involved young patients with MD who are still in development. We acknowledge that an investigation of the development of cognitive problems over time, and in particularly study of possible changes related to aging, would require longitudinal data.

Limitations of our study are the heterogeneity regarding age and the unequal size of patient groups, which may have lowered the power of our study. Still, the effect size for the difference between the *SGCE* + and *SGCE*- group on the emotion recognition test was large, which indicates that this finding is clinically relevant. We tested planning as part of executive functioning in children even under the age of 8 years, while the test offers standardized scores for children from 8 years and older. Planning is still in development in children, which means that the test might not be suitable for this age group. Hence, we re-ran the analyses without children under the age of 8 years, but the results remained unchanged.

Based on our current study we can tentatively conclude that young patients with MD have no major cognitive impairment compared to healthy controls. MD *SGCE* + patients seem to be vulnerable to social cognition problems. Further research needs to investigate additional aspects of social cognition in this patient group. Also, this may be an indication of suboptimal development of other prefrontally regulated functions such as executive function, which may become more manifest at an older age when they will be maximally required. Overall, it seems that the motor problems are more severe than cognitive problems but clinicians need to keep in mind that especially social cognition can be affected. Executive problems may only develop later in life. If there are concerns about cognitive development of an individual patient, neuropsychological testing is necessary.

Duplicate publication and copyright

We declare that the submitted study and its essential substance have not previously been published and are not being considered for publication elsewhere. We declare that the submitted study is our own work and that copyright has not been breached in seeking its publication.

Declaration of competing interest

We declare that the submitted study and its essential substance have not previously been published and are not being considered for publication elsewhere. We declare that the submitted study is our own work and that copyright has not been breached in seeking its publication.

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