Received: 30 July 2024 | Accepted: 20 November 2024

DOI: 10.1111/dmcn.16214

ORIGINAL ARTICLE

Natural history of *SGCE*-associated myoclonus dystonia in children and adolescents

Valeria De Francesch[1,2,*] | **Ana Cazurro-Gutiérrez**[2,3,*] | **Elze R. Timmers**[4] | **Gemma Español-Martín**[3,5,6] | **Julia Ferrero-Turrión**[2] | **David Gómez-Andrés**[2,5] | **Anna Marcé-Grau**[2] | **Lucía Dougherty-de Miguel**[2,5] | **Victoria González**[2,5] | **Antonio Moreno-Galdó**[3,5,7] | **Marina A. J. Tijssen**[4,8] | **Belén Pérez-Dueñas**[2,3,5,6,8]

[1]Child and Adolescent Neuropsychiatry Unit, AULSS1 Dolomiti, San Martino Hospital, Belluno, Italy

[2]Innovative Therapies in Pediatric Neurology Research Group, Vall d'Hebron Research Institute, Barcelona, Spain

[3]Department of Pediatrics, Universitat Autònoma de Barcelona, Barcelona, Spain

[4]Expertise Centre Movement Disorders Groningen, Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

[5]Department of Pediatrics, Pediatric Neurology and Psychiatry, Vall d'Hebron Hospital, Barcelona, Spain

[6]Biomedical Research Networking Center on Rare Diseases, Madrid, Spain

[7]Biomedical Research Networking Center on Mental Health, Madrid, Spain

[8]European Reference Network for Rare Neurological Diseases, Tübingen, Germany

Correspondence
Belén Pérez-Dueñas, Vall d'Hebron Institut de Recerca, Vall d'Hebron Hospital Universitari, Universitat Autònoma de Barcelona, Passeig Vall d'Hebron 119, 08035 Barcelona, Spain.
Email: belen.perez@vhir.org; belen.perez.duenas@uab.cat

Funding information
Myoclonus Dystonia Spanish association (ALUDME), Grant/Award Number: FORT23/00034, PI24/01083 and PI21/00248; Agència de Gestió d'Ajuts Universitaris i de Recerca, Grant/Award Number: 2022 FI_B 00996; Instituto de Salud Carlos III, Grant/Award Number: FORT23/00034, PI21/00248 and PI24/01083

Abstract

Aim: To investigate the natural progression of *SGCE*-associated myoclonus dystonia from symptom onset in childhood to early adulthood.

Method: Myoclonus and dystonia were monitored using rating scales in two cohorts of participants from Spain and the Netherlands. Individual annualized rates of change were calculated and longitudinal trends were assessed using Bayesian mixed models. Psychiatric features were evaluated cross-sectionally in the Spanish cohort.

Results: Thirty-eight patients (21 males, 17 females) were evaluated at a mean age (SD) of 10 years (4 years 7 months; range 2–21 years) and 14 years 2 months (4 years 8 months; range 4–25 years). We observed a significant worsening of action myoclonus, global dystonia, and dystonia during writing (mean annual increases of 1.356, 0.226, and 0.518 in the Unified Myoclonus, Burke–Fahn–Marsden, and Writer's Cramp Rating Scales respectively). Accordingly, participants perceived a significant worsening in their speech, writing, and walking abilities. Twenty-six of 32 participants suffered from anxiety ($n = 13$), obsessive-compulsive disorder ($n = 9$), and attention-deficit/hyperactivity disorder ($n = 8$).

Interpretation: This study demonstrates that, unlike in the adult population, myoclonus dystonia syndrome in childhood and adolescence follows a progressive course that can be debilitating in the early stages of life. These findings, along with a high prevalence of psychiatric symptoms, highlight the need for early therapeutic interventions to prevent long-term motor and psychological sequelae.

This original article is commented by Tarrano and Worbe on pages 695–696 of this issue.

Abbreviations: BFMDRS, Burke–Fahn–Marsden Dystonia Rating Scale; GDRS, Gait Dystonia Rating Scale; OCD, obsessive-compulsive disorder; UMRS, Unified Myoclonus Rating Scale; WCRS, Writer's Cramp Rating Scale; WCRS+S, Writer's Cramp Rating Scale + Shoulders.

*These authors are both first authors of this manuscript and contributed equally to the work.

Plain language summary: https://onlinelibrary.wiley.com/doi/10.1111/dmcn.16230

Myoclonus dystonia caused by mutations in ε-sarcoglycan (*SGCE*) is a childhood-onset neurological disorder characterized by myoclonus, dystonia, and psychiatric features.[1] *SGCE*-associated myoclonus dystonia is an autosomal dominant disease with reduced penetrance because of maternal imprinting.[2]

Although typically manifesting in childhood, there is limited information on clinical manifestation in children. To address this knowledge gap, our group recently published two cross-sectional studies that analysed the early signs of myoclonus[3] and dystonia[4] in children and adolescents with *SGCE*-associated myoclonus dystonia. In these cohorts, myoclonus was universally present and increased in severity during action tasks such as speaking, feeding, writing, or walking.[3] Action dystonia was also present in most children when writing and during walking.[4]

In clinical practice, we observed a progression of motor symptoms in some children from our cohort, which required pharmacological interventions and deep brain stimulation early in life.[5] On the other hand, other authors observed a spontaneous motor improvement during the first years of life, thus discouraging surgical interventions at this age.[1] These conflicting results highlight the need for a prospective study to understand the natural history and prognosis of the disease from the very early stages to establish early and effective interventions.

Clinimetric tools are essential to monitor disease progression. This group has previously demonstrated the effectiveness of three subscales of the Unified Myoclonus Rating Scale (UMRS), that is, the questionnaire (I), the action myoclonus (IV), and functional (V) tests, to quantify myoclonus severity in *SGCE*-associated myoclonus dystonia.[3] Additionally, a modified version of the Writer's Cramp Rating Scale (WCRS), which includes the proximal muscles of the shoulder (WCRS+S), was validated to rate the severity of writing dystonia in patients older than 5 years.[4] Moreover, we developed the Gait Dystonia Rating Scale (GDRS) to assess dystonia during walking and running.[4] The WCRS+S and the GDRS showed a strong correlation with the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS), enhancing the convergent validity of both scales. Finally, the UMRS questionnaire allowed the quantification of disability in activities of daily living for the first time in the paediatric population.[6,7]

Psychiatric symptoms are highly prevalent in adult patients with *SGCE*-associated myoclonus dystonia.[6,8,9] In the only natural history study on adult patients with *SGCE* disorders, panic disorder and depression were more prevalent during the course of the disease.[9] However, studies on psychiatric manifestations in children with *SGCE*-associated myoclonus dystonia are scarce and, to our knowledge, have not been analysed separately from adults.

Given this background, this study aimed to describe the natural history of *SGCE*-associated myoclonus dystonia in children and adolescents. We used the aforementioned rating scales to rate the progression of myoclonus and dystonia, and changes in disability for activities of daily living. In parallel, we assessed the prevalence and typology of psychiatric disorders during the study period.

What this paper adds

- Children and adolescents with *SGCE*-associated myoclonus dystonia showed a progression of motor symptoms.
- Children developed a significant increase in the severity of axial and limb myoclonus, as well as dystonia during writing.
- Children reported a marked decline in their speech, writing, and walking abilities.
- Up to 74% of children had a psychiatric diagnosis, most commonly anxiety, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder.

METHOD

Two cohorts of patients from the Vall d'Hebron Research Institute (Barcelona, Spain) and the Expertise Centre Movement Disorders Groningen, University Medical Center Groningen (the Netherlands) were included in the study based on the following criteria: (1) age younger than 22 years at first assessment; (2) presence of *SGCE* pathogenic variants; (3) follow-up of over 24 months between the first and last evaluation; and (4) assessment using a standardized video-recording protocol.

Participants were excluded if they had received deep brain stimulation before recruitment or during the study period, or if they refused to participate or continue in the study.

Written informed consent was obtained from all participants. The Ethics Committee of Vall d'Hebron University Hospital approved the study (approval no. PR(AMI)205/2021).

Clinical assessment

The study was conducted between 2014 and 2023. The research visits were aligned with scheduled medical appointments. During these visits, data on the participant's family, as well as data on the participant's neurodevelopment, their medical history, handedness, and medication were collected. Additionally, motor assessments were conducted and recorded using a video-recording protocol (Appendix S1).

A paediatric neurologist (VDF), who was blinded to the clinical status of participants, rated all participants using the video-recorded material. Before rating, a calibration process for each scale was conducted between two examiners (VDF and BPD) using a sample of eight patients with *SGCE*-associated myoclonus dystonia who were not included in the study.

To assess myoclonus, the UMRS[10] subscales for myoclonus at rest (II), myoclonus during action (IV), and functional tests (V) were used. Dystonia was assessed using the BFMDRS motor subscale, the WCRS+S for the dominant hand in patients older than 5 years, and the GDRS.[4]

A functional Disability Questionnaire (Appendix S1) combining items from both the UMRS and BFMDRS was designed to evaluate the impact of myoclonus and dystonia on 11 activities of daily living. Each item was rated from 0 (no disability) to 4 (maximum disability), with total scores ranging from 0 to 44. The questionnaire included a global disability evaluation provided by the patient (score 0–4).

In the Spanish cohort, psychiatric evaluations were performed by a child psychiatrist; diagnoses were made using the Kiddie Schedule for Affective Disorders and Schizophrenia Parent, Lifetime Version.[11] This semi-structured interview assesses current and past psychopathology in school-age children according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.[12] Psychiatric diseases were also assessed based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[13]

Statistical analysis

Descriptive data for quantitative variables included the mean, SD, total range, and median; frequencies and percentages were used for qualitative variables. The individual evolution of each participant across all measured scales was represented using spaghetti plots.

For missing data in the rating scales, the following statement was applied to each subscale: when two or fewer items were missing, the values were inserted as the rounded mean of the items with a valid score. If more than two items were missing, the participant was excluded from the subscale analysis.

We assessed the differences between the first and last evaluation using two complementary approaches. First, we estimated the effect of time using Bayesian mixed-effect models with a Markov chain Monte Carlo method.[14] Second, we calculated an annualized rate of change for each scale for every individual (last evaluation minus first evaluation divided by the time between evaluations in years) and represented its distribution using raincloud plots.[15] This data analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria) and specific packages for Bayesian mixed-effects models. Additionally, paired Student's *t*-tests were used to compare individual items of the rating scales.

RESULTS

Demographic data

The initial cohort consisted of 44 participants; six participants were excluded because they had undergone globus pallidus internus deep brain stimulation before the second assessment. Thus, a total of 38 patients (21 males; 17 females) were included in this study (Table S1). Mean (SD) age at first evaluation was 10 years (4 years 7 months; range 2–21 years) and 14 years 2 months (4 years 8 months; range 4–25 years) at the last evaluation. The mean (SD) follow-up was 4 years 1 month (1 year 1 month) and mean (SD) disease duration at the last evaluation was 11 years 5 months (4 years 11 months). All participants had typical neurodevelopment, except for one participant with language delay and mild intellectual disability.

Presenting symptoms at onset ($n = 38$) were myoclonus in 22 participants (58%), dystonia in five (13%), and both myoclonus and dystonia in 11 (29%). Myoclonus onset ($n = 33$) occurred at a mean (SD) age of 2 years 7 months (1 years 7 months; range 6 months–10 years); dystonia onset ($n = 16$) was 3 years (2 years 5 months; range 11 months–12 years). Handedness was known in 38 patients; 32 (84%) were right-handed. Two participants were forced to switch handedness because of disabling dystonia.

Oral medication to control motor symptoms was used in 22 of 38 patients (58%); eight received a single drug, five received two drugs, and nine tried three or more drugs. These included zonisamide ($n = 12$), clonazepam ($n = 12$), levodopa ($n = 9$), trihexyphenidyl ($n = 8$), levetiracetam ($n = 5$), piracetam ($n = 2$), oxcarbazepine ($n = 1$), propranolol ($n = 1$), brivaracetam ($n = 1$), and oxybutynin ($n = 1$). Therapies were often discontinued because of lack of efficacy or side effects.

One participant received a botulinum neurotoxin A injection to the lower limbs without significant improvement.

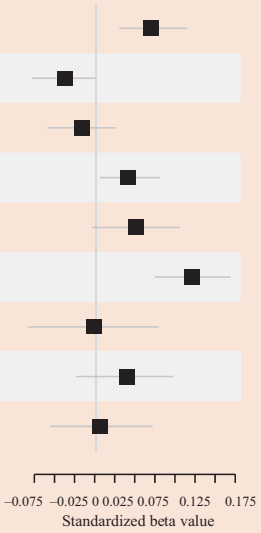
Motor assessment

The WCRS+S, GDRS, BFMDRS, and UMRS had less than 5% of missing data. Videos were not available for two participants in the WCRS, four in the GDRS, three in the BFMDRS, and 11 in the UMRS. Eight children under 6 years old could not be rated for writing and drawing of the Archimedes spiral (Table S2).

The UMRS action subscale identified myoclonus in all examined participants at the first evaluation ($n = 31$), showing a clear worsening at follow-up reflected by a mean annual increase of 1.36 per year (95% confidence interval [CI] = 0.836–1.906; $p = 0.001$) (Table 1 and Figure 1). Worsening was significant in the trunk ($p = 0.009$), upper limbs (right arm: $p = 0.007$; left arm: $p = 0.02$), and lower limbs (right leg: $p = 0.041$; left leg: $p = 0.004$) (Figure 2).

TABLE 1 Mean annualized change for each rating scale.

Scale	Posterior mean annualized change 95% HPD credible interval	pMCMC
Writer's Cramp Rating Scale	0.518 (0.221; 0.857)	0.012
Gait Dystonia Rating Scale (walking)	−0.132 (−0.271; 0.001)	0.056
Gait Dystonia Rating Scale (running)	−0.083 (−0.287; 0.121)	0.390
Burke–Fahn–Marsden Rating Scale (motor)	0.226 (0.031; 0.451)	0.044
Unified Myoclonus Rating Scale (rest)	0.307 (−0.029; 0.635)	0.058
Unified Myoclonus Rating Scale (action)	1.356 (0.836; 1.906)	0.001
Unified Myoclonus Rating Scale (functional tests)	–0.005 (–0245; 0.420)	0.908
Disability Questionnaire	0.170 (–0.105; 0.420)	0.208
Autoevaluation of Global Disability	0.004 (–0.041; 0.051)	0.878



Data are shown as mean annualized change (95% confidence interval [CI]). Black squares indicate mean change and error bars indicate 95% CI. pMCMC (particle Markov chain Monte Carlo) represents an analogue of the *p*-value.

Abbreviation: HPD, highest probability density.

The UMRS rest subscale identified myoclonus in most participants at first evaluation ($n = 21$ of 33), with an annual worsening of 0.307 (95% CI = −0.029 to 0.635; $p = 0.058$). When analysing body parts separately, we observed a significant worsening of myoclonus at rest in the neck ($p = 0.021$) and right arm ($p = 0.025$).

The UMRS functional tests ($n = 29$) showed a non-significant annual change of −0.005 points (95% CI = −0.245 to 0.228; $p = 0.908$), although worsening was significant for handwriting ($p = 0.016$) and the soup spoon task ($p = 0.02$).

All evaluated participants ($n = 35$) exhibited dystonic features on the BFMDRS motor scale. At follow-up, we observed a significant mean annual increase of 0.226 (95% CI = 0.031–0.451; $p = 0.044$), this being significant for the upper limbs (right arm: $p = 0.043$; left arm: $p = 0.037$).

The WCRS identified writing dystonia in almost all evaluated participants ($n = 23$ of 24), with writing dystonia present from the acquisition of the writing task in all cases. A significant annual increase of 0.518 points was observed (95% CI = 0.221–0.857; $p = 0.012$). Worsening of dystonic posturing was significant for the shoulders ($p < 0.001$) and elbows ($p < 0.001$). Two participants switched hand dominance because of worsening dystonia. Five patients used a sensory trick during writing, consisting of touching the pen or the writing hand with the other hand or the face (Figure 3).

The GDRS detected gait dystonia during walking and running in 17 of 34 and 17 of 24 participants respectively at the first evaluation (Figure 4). Gait dystonia improved over time, with a non-significant mean annual decrease of −0.132 during walking (95% CI = −0.271 to 0.001; $p = 0.056$) and −0.083 during running (95% CI = −0.287 to 0.121; $p = 0.39$) Thirteen of 34 participants used sensory tricks during walking and 5 of 24 during running.

Sensory tricks during writing, and during walking and running, were unchanged in four participants and appeared inconsistently in 14, either at the first or last assessment.

No differences were observed between participants with truncating ($n = 25$) and non-truncating ($n = 7$) variants in *SGCE*, or between males and females.

Disability assessment

In 35 patients, the questionnaire showed a non-significant annual increase of 0.17 (95% CI = −0.105 to 0.42; $p = 0.208$). When analysing items independently, progression was significant for speaking ($p = 0.01$), writing ($p = 0.002$), and walking ($p = 0.021$).

The global disability evaluation provided by patients ($n = 25$) did not show significant changes on how they perceived their impairment across the study period (mean annual increase: 0.004; 95% CI = −0.041 to 0.051; $p = 0.878$).

Neuropsychiatric features

Thirty-one participants were screened for the presence of neuropsychiatric features; 23 (74%, 11 females, 12 males) were suspected to have a neuropsychiatric condition and were formally evaluated by a child psychiatrist during the study period, each receiving at least one neuropsychiatric diagnosis (Table S3). The most common was anxiety disorder ($n = 15$ of 31, nine females, six males), including generalized anxiety disorder ($n = 8$), specific phobia ($n = 4$), phagophobia

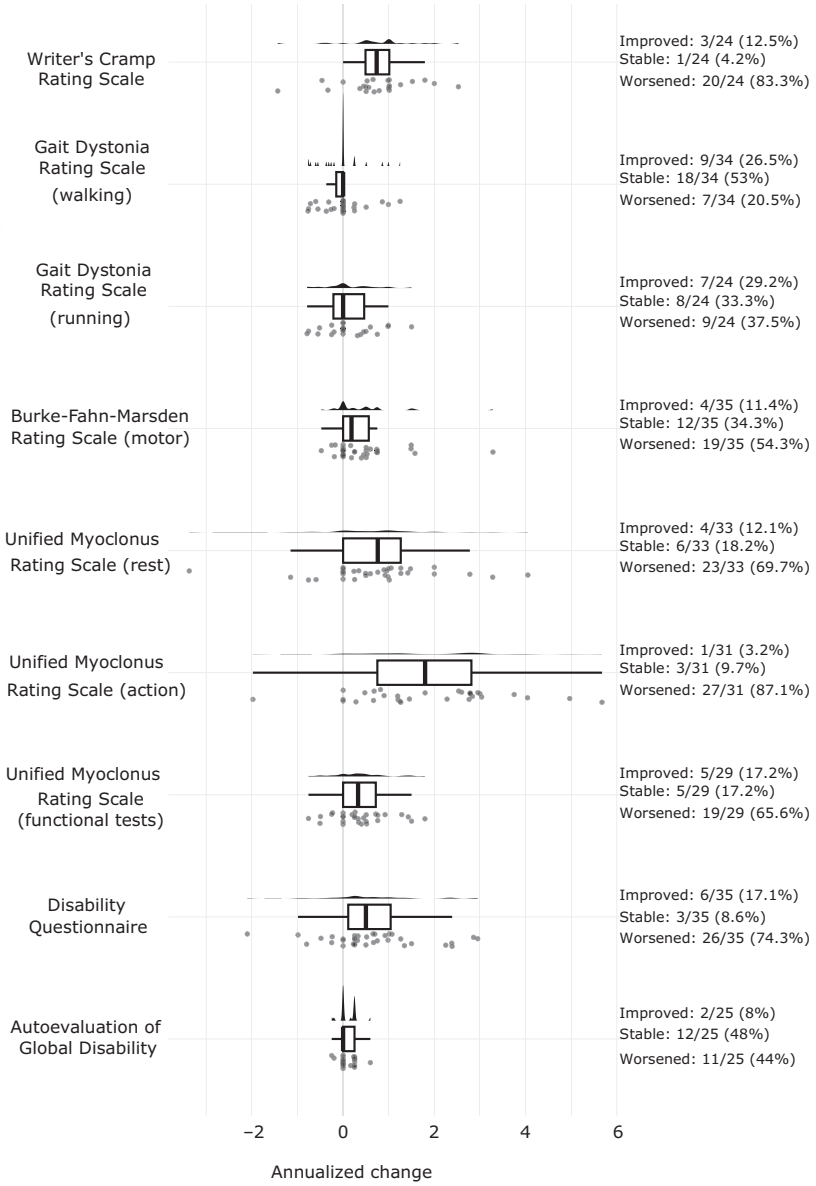


FIGURE 1 Raincloud plot depicting the participants' annual change in each rating scale. Each point represents the mean annual change of each participant. The density plot shows the overall distribution, while the box plot highlights the median and interquartile range.

($n=3$), entomophobia or fear of elevator ($n=1$), panic disorder ($n=1$), social phobia ($n=1$), and separation anxiety disorder ($n=1$). Other diagnoses were obsessive-compulsive disorder (OCD) ($n=9$ of 31, five females, four males), attention-deficit/hyperactivity disorder (ADHD) ($n=7$ of 31, one female, six males), either combined ($n=7$) or predominantly inattentive ($n=1$). Rarer disorders included motor tics ($n=3$), mild intellectual disability ($n=1$), encopresis or enuresis ($n=2$), behaviour disorder ($n=1$), adjustment disorder with depressed mood ($n=1$), and anorexia nervosa ($n=1$).

Specific learning disorders were identified in 10 participants (four females, six males); eight had an unspecified learning disorder and two had a reading disorder.

During the study period, oral medication was used in nine participants with neuropsychiatric symptoms, including stimulants ($n=4$), sertraline ($n=4$), and benzodiazepines ($n=2$).

DISCUSSION

In this study, we conducted a standardized protocol focused on the analysis of the natural history of motor symptoms in 38 paediatric patients with *SGCE*-associated myoclonus dystonia from two European reference centres for movement disorders. Given the rarity of the condition,[1,16] this longitudinal study is based on a relatively large cohort, providing a good representation of the disease.

To date, the only *SGCE*-associated myoclonus dystonia natural history study included adult patients with a mean age of 44 years.[9] The authors observed stability of dystonia and myoclonus over time. However, there was a change in the body distribution of symptoms, with more participants having dystonia in the upper limbs and myoclonus in the neck and trunk compared with the baseline assessment,

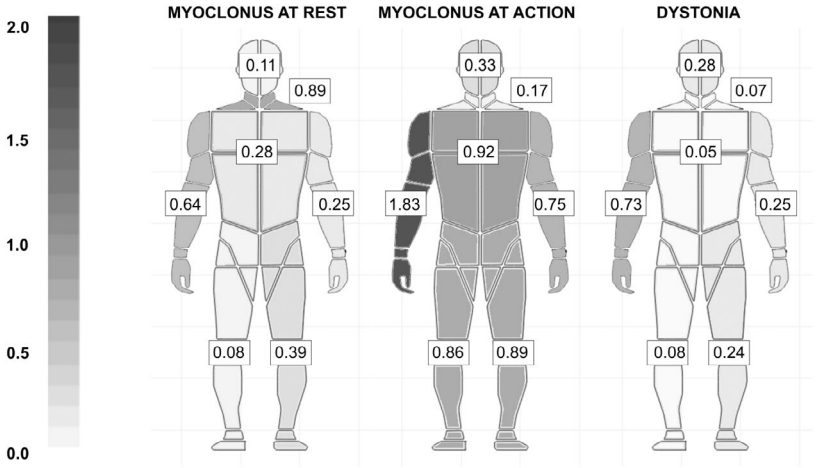


FIGURE 2 Graphic representation of the progression of myoclonus at rest (Unified Myoclonus Rating Scale, at rest subscale) and during action (Unified Myoclonus Rating Scale, during action subscale), and dystonia (Burke–Fahn–Marsden Rating Scale, motor subscale) in different body parts. The number inside each box represents the mean difference between the first and last evaluation. The greyscale indicates the severity of the change, ranging from white to dark grey, with white representing the least worsening and dark grey representing the greatest worsening of myoclonus and dystonia.

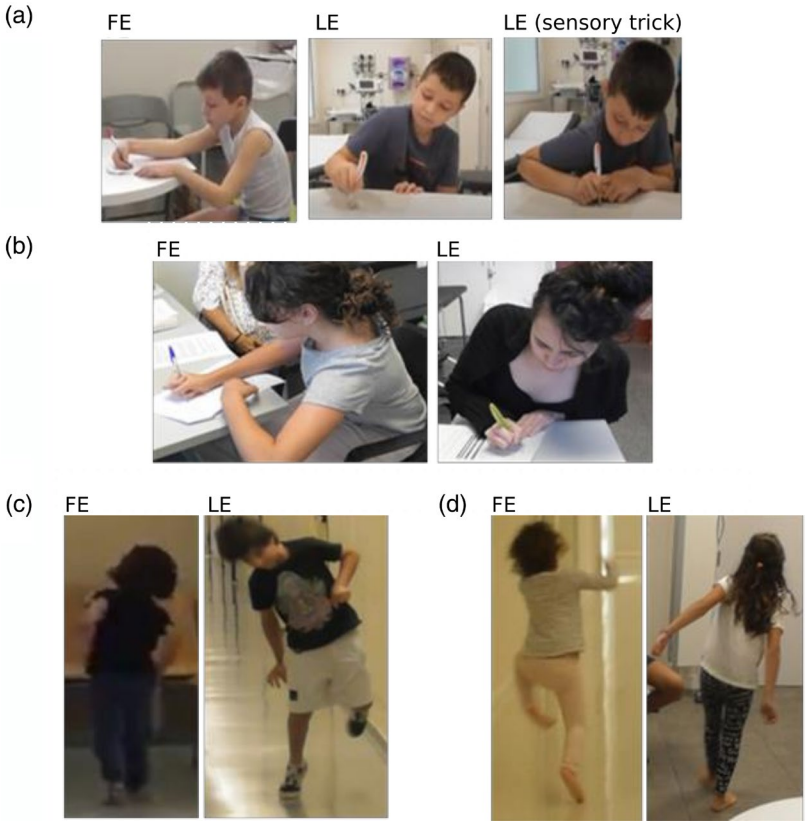


FIGURE 3 Frame capture showing progression of writing and gait dystonia in four participants from the cohort. (a) P9 (first evaluation [FE] 18; last evaluation [LE] 26). (b) P19 (first evaluation 28; last evaluation 32). (c) P27 (first evaluation 10; last evaluation 8). (d) P12 (first evaluation 15; last evaluation 12).

in agreement with previous observations.[17] Progression during childhood and adolescence has never been systematically studied; however, it is crucial to determine when and how therapeutic interventions should be implemented to promptly initiate treatments that can mitigate long-lasting sequelae.

Myoclonus and dystonia

Our primary findings, after an average follow-up of 4 years, show a significant increase in the severity of axial and limb myoclonus, and dystonia when writing. Consequently, participants reported a marked decline

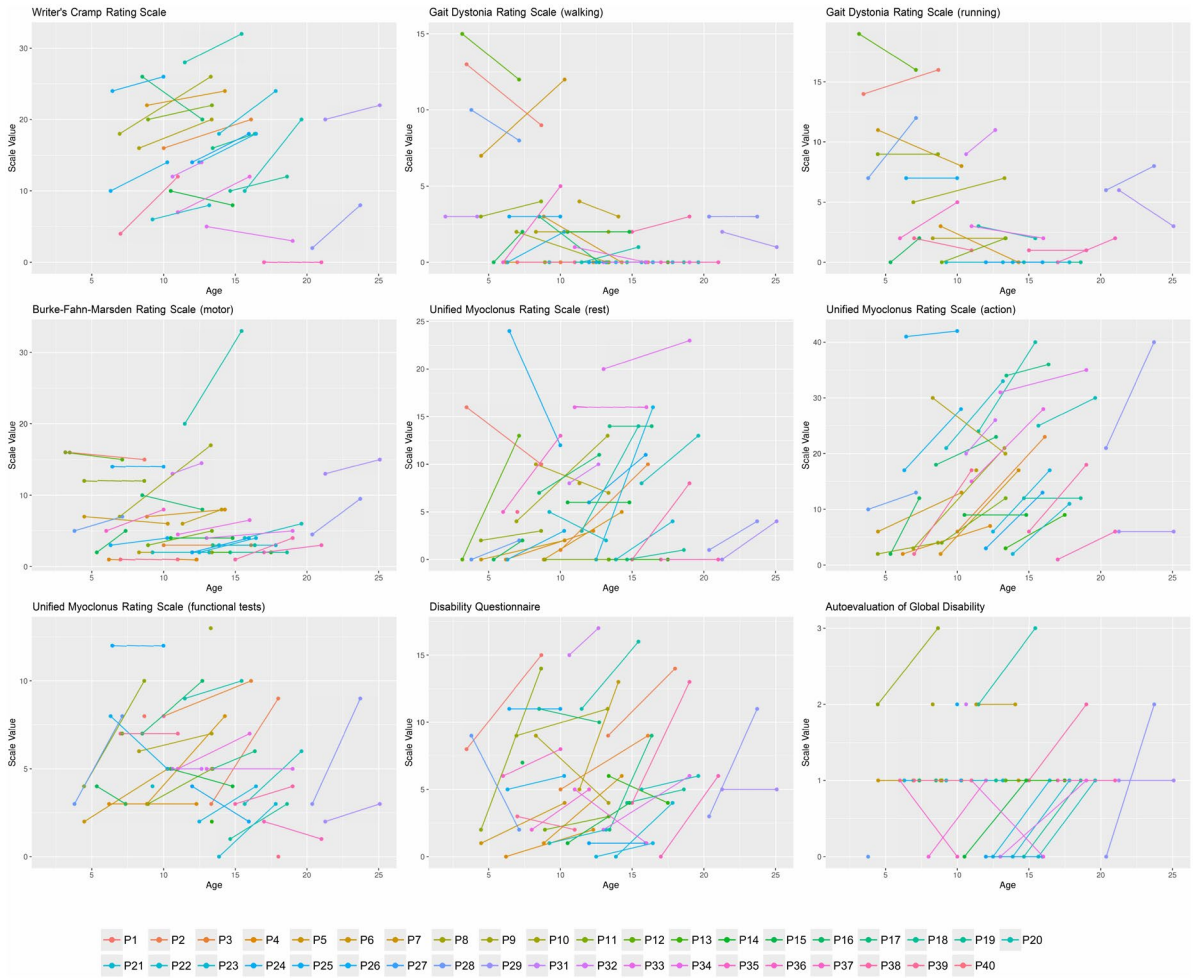


FIGURE 4 Representation of the rating scale scores at the first and last evaluation for all the participants in the cohort. The axes represent the age at which each of the 38 patients was evaluated (x axis) and the score at each visit (y axis). The range values of each rating scale are as follows: Writer's Cramp Rating Scale (0–32); Gait Dystonia Rating Scale for walking and running (0–20); Burke–Fahn–Marsden Rating Scale (0–120); Unified Myoclonus Rating Scale (at rest) (0–128); Unified Myoclonus Rating Scale (during action) (0–160); Unified Myoclonus Rating Scale (functional tests) (0–28); Disability Questionnaire (0–44); Auto Evaluation of Global Disability (0–4).

in their speech, writing, and walking abilities. Based on this, we recommend that children with *SGCE*-associated myoclonus dystonia should be promptly referred to occupational therapists to prevent any adverse effects on their academic performance, physical activities, and other aspects of daily living.

In this cohort, myoclonus was present in all participants at the initial evaluation. At the follow-up, we observed a significant increase in the severity of myoclonus during action in almost all body parts. Myoclonus at rest also progressed, although values did not reach statistical significance; 87%, 69.7%, and 65.5% of patients showed progression in the severity of myoclonus during action, rest, and functional tests respectively (Figures 1 and 3). Consistent with these observations, previous studies also noted a progressive course of myoclonus in the first decades of life.[18,19] Taken together, these findings confirm that *SGCE*-associated myoclonus is a progressive symptom during childhood and adolescence.

We evaluated the progression of dystonia using different clinimetric methods. Apart from the BFMDRS, we also used goal-directed scales for action dystonia during essential activities in childhood, such as writing, walking, and running. The BFMDRS showed a significant progression of dystonia, which was particularly significant for the upper limbs. In agreement with this, the WCRS identified a worsening of writing dystonia in 83% of participants. However, the GDRS did not identify significant changes in gait dystonia. Indeed, 53% of participants exhibited no changes in dystonic features while walking and 26.5% showed improvement. This finding aligns with previous studies reporting that dystonia remains stable[17] or can even spontaneously improve in the lower limbs in some children, even as myoclonus worsens simultaneously.[18–20]

The reasons why dystonia and myoclonus progress in children and adolescents and stabilize in adults may be linked to the higher motor and metabolic demands of the developing brain, as in many other childhood-onset neurogenetic and neurometabolic diseases. Also, an explanation for the progression of dystonia in the upper body regions but not in the lower limbs may be linked to the activity of motor circuits

involved in different physical activities depending on age. In fact, the age of individuals significantly affects the body distribution of symptoms in other forms of genetic dystonia. For example, children with *TOR1A*-associated dystonia usually present with gait dystonia and lower-limb involvement, whereas family members with later onset tend to have arm dystonia in the form of writer's cramp.[21] It is also well known that use-dependent plasticity may become detrimental and produce dystonia when practice and repetition are excessive, and when predisposing conditions are present.[22]

The Disability Questionnaire did not identify significant changes over time, although 74% of participants obtained worse scores at the follow-up. We believe that disability questionnaires are challenging in the paediatric population because typical neurodevelopment results in a gain of functionality when performing activities of daily living over the years. This could have masked the perceived progression of disability related to *SGCE*-associated myoclonus dystonia symptoms in the children from this study. Remarkably, when evaluating tasks separately, participants reported a significant deterioration in speaking, writing, and walking, which aligns with the progression in severity of myoclonus and dystonia captured by the motor rating scales, and underlines the negative long-term consequences that motor symptoms may have on the quality of life of these children.

In *SGCE*-associated myoclonus dystonia, speech impairment has been described exceptionally.[23,24] However, speech difficulties were reported by 15 (39%) of the participants in this cohort, and participants had significant worsening of speech over time. Speech problems resulted mostly from pauses in the voice caused by speech-induced myoclonus, but also from reduced voice volume caused by vocal cord dystonia and impaired articulation related to oromandibular dystonia.

Interestingly, we identified several natural history developmental profiles in participants with *SGCE*-associated myoclonus dystonia (Figure 4). Genetic heterogeneity (at least 15 different genetic variants were identified in participants from this study) can produce different molecular mechanisms that mediate changes in *SGCE* function at the synapse, thus contributing to clinical heterogeneity. Also, epigenetic and environmental factors may modify the expression of clinical features, as worsening of symptoms in patients triggered by fever, infections, and stress that we observed in clinical practice. Thus, some participants had outlier scores in their motor scales, whose impact was minimized by using robust statistical Markov chain Monte Carlo-adjusted Bayesian models.

Neuropsychiatric features

Neuropsychiatric features are considered part of the disease phenotype in adulthood.[7] Their course was analysed in an adult cohort,[9] showing an increase in the prevalence of panic disorder and depression over time. Yet, data on the frequency and manifestation of neuropsychiatric symptoms in childhood are sparse and are typically derived from a small number of patients in broader cohorts that predominantly consist of adults.[7,25] Bearing in mind these precedents, our study included a cross-sectional analysis of neuropsychiatric manifestations as a secondary objective.

Remarkably, a high prevalence of psychiatric features (over 70%) was found in our paediatric cohort. The most common was anxiety disorder, followed by OCD and ADHD. Specifically, OCD and anxiety disorders were extremely frequent compared to their prevalence in the paediatric population.[26] Also, anxiety, specific phobias, and obsessive thoughts had a pervasive effect on all contexts of activities of daily living, requiring pharmacological and other therapeutic interventions in most participants. Therefore, focusing attention on psychiatric features is mandatory to monitor symptoms and to provide early multidisciplinary treatments. For example, ADHD and OCD in adolescence could promote uncontrolled and impulsive consumption of alcohol and other drugs. In fact, alcohol dependence is a common finding in adults with *SGCE*-associated myoclonus dystonia.[27–29] These psychiatric problems, together with motor disability, can be potential factors for a poorer quality of life.

We also observed a high prevalence of specific learning disorders (26%). These findings, together with psychiatric manifestations and difficulties with handwriting caused by motor symptoms, can have a great impact on school performance. Therefore, it is important to test all children with *SGCE*-associated myoclonus dystonia for learning and cognitive skills, as well as neuropsychiatric symptoms and fine motor difficulties in the first years of school, and to perform adaptive interventions to avoid academic failure.

Study limitations

The small sample size in this study resulted in less robust outcomes in many of the statistical tests. Rating scales were evaluated in most, but not all, participants (77%–92%). Because of their young age, some participants were uncooperative during the assessment or could not be evaluated for some functional tests or questions, such as writing, dressing, or hygiene. In a few instances, the questionnaire was answered by parents at the first evaluation and by children at the last evaluation, introducing a potential bias due to the change of respondents. A single rater scored all participants; therefore, no interrater agreement was calculated, hampering the reliability of the analysis. Moreover, although the rater was blinded to the clinical status of participants, changes in physical appearance due to growth may have facilitated the identification of the different assessment points.

Psychiatric features were not longitudinally assessed and some diagnoses were incomplete because of the complexities of diagnosing psychiatric conditions in paediatric patients.

Regarding the statistical analysis, this study included two formal assessments per participant. However, clinical rating scales do not necessarily reflect real-world situations as data are collected at a single point in time, making day-to-day fluctuations a significant issue. Moreover, patients with *SGCE*-associated myoclonus dystonia may become very anxious

during medical visits, manifesting an increase in myoclonic and dystonic movements compared to their baseline state. These fluctuations in symptoms may affect the assessments and potentially cause discrepancies between patient self-assessment of disability and exam-based measures conducted by researchers. Additionally, the follow-up period was not homogeneous among participants. To compensate for this limitation, the effect of time was estimated using Bayesian mixed-effect models. A 3- to 5-year follow-up is insufficient to fully understand the natural history of the disease; future studies should include annual assessments over a longer period to provide a more accurate estimation of disease progression.

Conclusions

This natural history study of *SGCE*-associated myoclonus dystonia confirms a progression in the severity of myoclonus and dystonia in childhood and adolescence, which can affect independence. These results are further supported by participants reporting increased impairment in writing, walking, and speech because of motor symptoms. Moreover, we demonstrate a high prevalence of psychiatric symptoms in paediatric patients, particularly anxiety disorders, OCD, and ADHD. Consequently, early interventions are needed to allow timely management of symptoms in this disorder.

ACKNOWLEDGEMENTS

BPD, DGA, VG, and MT are part of the European Reference Network for Rare Neurological Diseases. ACG was supported by the Agency for Management of University and Research Grants (no. 2022 FI_B 00996). AMG is granted a postdoctoral contract funded by Instituto de Salud Carlos III through the FORT23/00034 project. The study was funded by the Instituto de Salud Carlos III (nos. PI21/00248 and FORT23/00034), and by the Myoclonus Dystonia Spanish association (ALUDME).

DATA AVAILABILITY STATEMENT

The original data presented in the study are included in the article/Supporting Information. Further inquiries can be directed to the corresponding author.

ORCID

Belén Pérez-Dueñas https://orcid.org/0000-0002-4979-2788

REFERENCES

1. Roze E, Lang AE, Vidailhet M. Myoclonus-dystonia: classification, phenomenology, pathogenesis, and treatment. Curr Opin Neurol. 2018 Aug;31(4):484–90.
2. Grabowski M, Zimprich A, Lorenz-Depiereux B, Kalscheuer V, Asmus F, Gasser T, et al. The epsilon-sarcoglycan gene (SGCE), mutated in myoclonus-dystonia syndrome, is maternally imprinted. Eur J Hum Genet. 2003 Feb;11(2):138–44.
3. Vanegas MI, Marcé-Grau A, Martí-Sánchez L, Mellid S, Baide-Mairena H, Correa-Vela M, et al. Delineating the motor phenotype of SGCE-myoclonus dystonia syndrome. Parkinsonism Relat Disord. 2020 Nov; 80:165–74.
4. Correa-Vela M, Carvalho J, Ferrero-Turrión J, Cazurro-Gutiérrez A, Vanegas M, Gonzalez V, et al. Early recognition of SGCE-myoclonus-dystonia in children. Dev Med Child Neurol. 2023 Feb;65(2):207–14.
5. Candela S, Vanegas MI, Darling A, Ortigoza-Escobar JD, Alamar M, Muchart J, et al. Frameless robot-assisted pallidal deep brain stimulation surgery in pediatric patients with movement disorders: precision and short-term clinical results. J Neurosurg Pediatr. 2018 Oct;22(4):416–25.
6. Nardocci N. Myoclonus-dystonia syndrome. Handb Clin Neurol. 2011;100:563–75.
7. Peall KJ, Smith DJ, Kurian MA, Wardle M, Waite AJ, Hedderly T, et al. SGCE mutations cause psychiatric disorders: clinical and genetic characterization. Brain. 2013 Jan;136(Pt 1):294–303.
8. Timmers ER, Smit M, Kuiper A, Bartels AL, van der Veen S, van der Stouwe AMM, et al. Myoclonus-dystonia: Distinctive motor and non-motor phenotype from other dystonia syndromes. Parkinsonism Relat Disord. 2019 Dec;69:85–90.
9. Timmers ER, Peall KJ, Dijk JM, Zutt R, Tijssen CC, Bergmans B, et al. Natural Course of Myoclonus-Dystonia in Adulthood: Stable Motor Signs But Increased Psychiatry. Mov Disord. 2020 Jun;35(6):1077–8.
10. Frucht SJ, Leurgans SE, Hallett M, Fahn S. The Unified Myoclonus Rating Scale. Adv Neurol. 2002;89:361–76.
11. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997 Jul;36(7):980–8.
12. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Arlington, VA: American Psychiatric Association, 2000.
13. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association, 2013.
14. Hadfield JD. MCMC Methods for Multi-Response Generalized Linear Mixed Models: The MCMCglmm R Package. Journal of Statistical Software. 2010;33(2):1–22.
15. Allen M, Poggiali D, Whitaker K, Marshall TR, van Langen J, Kievit RA. Raincloud plots: a multi-platform tool for robust data visualization [version 2; peer review: 2 approved]. Wellcome Open Res 2021 Jan; 4(63).
16. LeDoux MS. Population Prevalence of Deleterious SGCE Variants. Tremor Other Hyperkinet Mov (N Y). 2020 Nov 4;10:50.
17. Peall KJ, Kurian MA, Wardle M, Waite AJ, Hedderly T, Lin JP, et al. SGCE and myoclonus dystonia: motor characteristics, diagnostic criteria and clinical predictors of genotype. J Neurol 2014; 261:2296–304.
18. Asmus F, Zimprich A, Tezenas Du Montcel S, Kabus C, Deuschl G, Kupsch A, et al. Myoclonus-dystonia syndrome: epsilon-sarcoglycan mutations and phenotype. Ann Neurol. 2002 Oct;52(4):489–92.
19. Nardocci N, Zorzi G, Barzaghi C, Zibordi F, Ciano C, Ghezzi D, et al. Myoclonus-dystonia syndrome: clinical presentation, disease course, and genetic features in 11 families. Mov Disord. 2008 Jan;23(1):28–34.
20. Roze E, Apartis E, Clot F, Dorison N, Thobois S, Guyant-Marechal L, et al. Myoclonus-dystonia: clinical and electrophysiologic pattern related to SGCE mutations. Neurology. 2008 Mar 25;70(13):1010–6.
21. Bressman SB, Sabatti C, Raymond D, de Leon D, Klein C, Kramer PL, et al. The DYT1 phenotype and guidelines for diagnostic testing. Neurology. 2000 May 9;54(9):1746–52.
22. Quartarone A, Ghilardi MF. Neuroplasticity in dystonia: Motor symptoms and beyond. Handb Clin Neurol. 2022;184:207–18.
23. Isaacs DA, Hedera P. Speech-activated Myoclonus Mimicking Stuttering in a Patient with Myoclonus-Dystonia Syndrome. Tremor Other Hyperkinet Mov (N Y). 2016 Jul 1;6:405.
24. Hjermind LE, Werdelin LM, Eiberg H, Krag-Olsen B, Dupont E, Sørensen SA. A novel mutation in the epsilon-sarcoglycan gene causing myoclonus-dystonia syndrome. Neurology. 2003 May 13;60(9):1536–9.
25. Peall KJ, Dijk JM, Saunders-Pullman R, Dreissen YE, van Loon I, Cath D, et al. Psychiatric disorders, myoclonus dystonia and SGCE: an international study. Ann Clin Transl Neurol. 2015 Nov 20;3(1):4–11.

26. Nazeer A, Latif F, Mondal A, Azeem MW, Greydanus DE. Obsessive-compulsive disorder in children and adolescents: epidemiology, diagnosis and management. Transl Pediatr. 2020 Feb;9(Suppl 1):S76–S93.
27. Kyllerman M, Forsgren L, Sanner G, Holmgren G, Wahlström J, Drugge U. Alcohol-responsive myoclonic dystonia in a large family: dominant inheritance and phenotypic variation. Mov Disord. 1990;5(4):270–9.
28. Quinn NP. Essential myoclonus and myoclonic dystonia. Mov Disord. 1996 Mar;11(2):119–24.
29. Gasser T, Bereznai B, Müller B, Pruszak-Seel R, Damrich R, Deuschl G, et al. Linkage studies in alcohol-responsive myoclonic dystonia. Mov Disord. 1996 Jul;11(4):363–70.

SUPPORTING INFORMATION

The following additional material may be found online:
Appendix S1: Video-recording protocol.
Table S1: Demographic data of the patients from the cohort.
Table S2: Score in the rating scales of every patient from the cohort.
Table S3: Neuropsychiatric features from all the patients of the cohort.

How to cite this article: De Francesch V, Cazurro-Gutiérrez A, Timmers ER, Español-Martín G, Ferrero-Turrión J, Gómez-Andrés D, et al. Natural history of *SGCE*-associated myoclonus dystonia in children and adolescents. Dev Med Child Neurol. 2025;67:740–749. https://doi.org/10.1111/dmcn.16214