Disease Burden and Functional Outcomes in Congenital Myotonic Dystrophy: A Cross-Sectional Study

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Disease burden and functional outcomes in congenital myotonic dystrophy
A cross-sectional study

ABSTRACT
Objective: Herein, we describe the disease burden and age-related changes of congenital-onset myotonic dystrophy (CDM) in childhood.

Methods: Children with CDM and age-matched controls aged 0 to 13 years were enrolled. Participants were divided into cohorts based on the following age groups: 0–2, 3–6, and 7–13 years. Each cohort received age-appropriate evaluations including functional testing, oral facial strength testing, neuropsychological testing, quality-of-life measurements, and ECG. Independent-samples t test or Wilcoxon 2-sample test was used to compare the differences between children with CDM and controls. Probability values less than 0.05 are reported as significant.

Results: Forty-one participants with CDM and 29 healthy controls were enrolled. The 6-minute walk was significantly different between CDM (258.3 m [SD 176.0]) and control participants (568.2 m [SD 73.2]). The mean lip force strength was significantly different in CDM (2.1 N [SD 2.8]) compared to control participants (17.8 N [SD 7.6]). In participants with CDM, the mean IQ (65.8; SD 18.4) was 3 SDs below the mean compared to standardized norms. Measurements of grip strength, sleep quality, and quality of life were also significantly different. Strength measures (oral facial strength, grip strength, and 6-minute walk) correlated with each other but not with participant IQ.

Conclusions: This work identifies important phenotypes associated with CDM during childhood. Several measures of strength and function were significantly different between participants with CDM and controls and may be useful during future therapeutic trials.

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GLOSSARY
CDM = congenital myotonic dystrophy; DM1 = myotonic dystrophy type 1; FVC = forced vital capacity; PDSS = Pediatric Daytime Sleepiness Scale; PedsQL = Pediatric Quality of Life Inventory; 6MWD = 6-minute walk test distance.

Myotonic dystrophy type 1 (DM1) is an autosomal dominant, multisystemic disorder that is caused by a CTGn repeat in the DMPK gene.1–3 Congenital myotonic dystrophy (CDM) represents the most severe form of myotonic dystrophy and results from a large expansion of the CTGn repeat between parent and child. Symptoms are present at birth and include severe hypotonia, respiratory failure, gastroparesis, and talipes equinovarus.4,5 These symptoms are distinct from those described in adults with DM1, who typically present with distal weakness, myotonia, and early-onset cataracts. During the first year of life, there is a 30% mortality for those infants ventilated for greater than 3 months.6 Beyond the first year of life, there is limited information about the natural history of CDM.

Clinically, children with CDM are observed to have significant improvement in respiratory and motor areas; however, as patients get older, myotonia, cardiac arrhythmias, and other features typical of adult-onset DM1 emerge. Both intellectual impairment and oral facial weakness cause significant burden during childhood.7,8 In addition to intellectual impairment, there is evidence of autism spectrum disorder and attention-deficit/hyperactivity disorder.7,9 A prior cross-sectional survey study identified difficulty with communication and problems with hands.

From the Departments of Neurology (N.E.J., R.B., K.B., D.D., M.D., E.P.), Orthopaedics (M.H., J.B.), and Physical Therapy (H.H.), and Division of Epidemiology (M.H., W.C.), The University of Utah, Salt Lake City; Department of Neurology (C.H.), The University of Rochester, NY; and Departments of Pediatrics, Clinical Neurological Sciences, and Epidemiology (C.C.), Western University, London, Canada. Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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and fingers as the issues that reduce quality of life in children. 10 While this work has helped to characterize the disease burden in children with CDM, it did not serially evaluate patients using clinical assessments.

The objectives of this study are 2-fold: first, to identify the disease burden associated with CDM in childhood at different ages; and second, to determine the feasibility and discriminatory ability of a set of relevant and commonly used outcome measures in this population.

METHODS Participants. Children with CDM between the ages of 0 and 13 years were enrolled at the University of Utah and Western University. All participants had (1) an onset of symptoms in the neonatal period requiring 72 hours or more of hospitalization, and (2) a history of hypotonia, respiratory failure, or feeding difficulty. In addition, participants were required to have genetic testing confirming a CTG repeat expansion in the DMPK gene greater than 200 repeats. Individuals were not included if they had any other non-DM1 illness or significant trauma within 1 month. Healthy controls were required to be ages 0 to 13 years with no other significant medical history or medication use.

Study procedures. All study procedures were conducted over a 2-day interval. Demographic data, medical history, and respiratory function were collected on all individuals.

Standard protocol approvals, registrations, and patient consents. All study procedures were approved by the institutional review board of both institutions.

Functional testing. The 6-minute walk was performed as previously described in children ages 3 to 13 years. 11 Maximum voluntary isometric contraction of hand grip was performed (JAMAR Plus; Sammons Preston). Lateral pinch was measured using the JAMAR Plus digital pinch gauge (Sammons Preston).

Oral facial testing. Both children with CDM and healthy controls received 2 quantitative measures of oral facial strength. A speech therapist with experience in these measures performed the training for both sites. The Iowa Oral Performance Instrument consists of a pressure bulb attached to a manometer. The pressure bulb was placed against the tongue and participants were asked to push the bulb to the alveolar ridge. Maximum pressure was averaged over 3 efforts. The Lip Force Meter was modified from prior study designs. A plastic mouth guard with the bite guard removed was attached to a force meter and was placed anterior to the teeth, with the lips closed around it. Participants were asked to hold the guard inside their mouths while the examiner applied steady force to remove it. The maximum force to remove the guard from the participants’ mouths was recorded, and averaged over 3 attempts.

Neuropsychological testing. Cognitive function in participants with CDM was assessed by an experienced neuropsychometrist or psychologist. Full-scale IQ was assessed using the Wechsler Preschool and Primary Scale of Intelligence (3rd edition) and the Wechsler Intelligence Scale for Children (4th edition) depending on age. Estimated IQ was assessed using the Wechsler Preschool and Primary Scale of Intelligence–III Block Design and Vocabulary or Receptive Vocabulary subtests, or the Wechsler Intelligence Scale for Children–IV Block Design and Vocabulary subtests. Control participants did not undergo neuropsychological assessment because of previously established norms. The Pediatric Sleep Questionnaire and the Pediatric Daytime Sleepiness Scale (PDSS) were used to evaluate sleep quality and daytime sleepiness in participants with CDM. Quality of life was assessed for participants with CDM using the Pediatric Quality of Life Inventory (PedsQL) parent proxy measure.

Cardiac testing. All children with CDM had a standard 12-lead ECG.

Respiratory testing. Forced vital capacity (FVC) measurements were attempted on 16 participants with CDM who were older than 6 years. The MIR Spirobank and the CareFusion MicroLab spirometers were used to collect FVC. FVC was calculated based on height, weight, age, and sex. A mouthpiece was used along with the open circuit method and verbal encouragement was given during rapid exhalation in an upright and seated position. Up to 6 trials were attempted per participant.

Gastrointestinal testing. Participants and parents were queried regarding the presence of abdominal pain association with food, diarrhea, constipation, and use of motility agents.

Statistical analyses. Descriptive statistics were conducted on the overall sample and the CDM and control groups. Independent-samples t test or Wilcoxon 2-sample test was used to compare the differences between groups on functional testing (6-minute walk and grip and pinch myometry), oral facial strength testing (lip force and tongue strength), and neuropsychological testing (IQ, PDSS, and PedsQL), adjusting for age and sex. All measures were evaluated by age, a high (≥1,000 CTG repeats) and low (<1,000 CTG repeats) group. Pearson correlation was performed to understand the relationships among IQ, 6-minute walk, lip force, and grip myometry. All analyses were conducted with SAS 9.4 statistical software (SAS Institute, Cary, NC). Probability values less than 0.05 were considered significant.

RESULTS Based on eligibility criteria, 43 children with CDM were identified. The study enrolled 41 children with CDM and 29 healthy controls. Mean age of the children with CDM was 6.8 years (SD 3.3) and the mean CTG repeat length was 1,200 (SD 500). Detailed demographic data, including age, sex, CTG repeat length, and respiratory status are provided in table 1.

Functional testing. Participants younger than 2 years did not participate in functional testing. For those older than 2 years, not all children with CDM were able to complete each task, either because they were nonambulatory (19.0%) or because behavioral difficulties limited their ability to complete the task (11.0%). On the 6-minute walk test distance (6MWD), children with CDM (n = 33) walked 258.3 m (SD 176), while healthy controls walked 568.3 m (SD 73.2) (p < 0.001). There are age-based normative values for children’s 6MWD. 12 Using these, children with CDM who were older than 5 years averaged the 1st percentile (SD 0.03; range 0%–12.7%), while children in the control group averaged ages 0.0 to 2.2 years (SD 0.01).
group were in the 24th percentile (SD 0.24; range 0%–95.3%). Older children in both cohorts walked longer 6MWD compared to younger children. There was not a decline in the distance walked in the CDM cohort with age (figure 1A). When comparing higher CTG repeat lengths ($\geq 1,000$) to lower CTG repeat lengths ($< 1,000$), there was no difference in 6MWD between the 2 groups (figure 1B). Children with CDM ($n = 29$) had a mean right grip strength of 5.3 kg (SD 4.5) compared to a right grip strength of 15 kg (SD 5.2) in healthy controls ($p < 0.001$). On right pinch strength, children with CDM ($n = 28$) had a mean of 1.7 kg (SD 1.2) compared to 4.4 kg (SD 1.3) ($p < 0.001$). There was a gradual improvement in grip and pinch strength with age regardless of CDM status (figure 1, C and E). There was no difference in how the lower and higher CTG repeat groups performed by age in grip and pinch strength (figure 1, D and F).

Neuropsychological testing. The mean estimated IQ among children with CDM was 65.8 (SD 18.4), which is 3 SDs below the mean compared to standardized norms. There was no clear improvement or decline in IQ by age or CTG repeat length (figure 3, A and B). On the PDSS, the measure of daytime sleepiness, the mean score was 11.9 (SD 6.48). There was an increase in daytime sleepiness with age and CTG repeat length (figure 3, C and D). The mean Pediatric Sleep Questionnaire score, a measure of sleep quality, was 24.2 (SD 8.83). There was a clear decline in sleep quality with age but not with CTG repeat length (figure 3, E and F). Finally, on the parent proxy PedsQL, the mean score was 56.3 (SD 15.0). There was a decline in quality of life with age in both groups, and no clear difference with CTG repeat length (figure 3, G and H).

Cardiac testing. There were 5 children with CDM who had cardiac issues, which were detected with ECG. These included left anterior fascicular block (1 child), prolonged QT (2 children), and first-degree AV block (2 children).

Respiratory testing. All participants were able to wean from respiratory support required during the neonatal period, and a minority required ongoing nighttime positive pressure ventilation (table 1). FVC measurements were attempted in children with CDM between the ages of 6 and 13 ($n = 16$). Thirty-eight percent of the children with CDM ($6/16$) were able to complete the spirometry testing when comparing those requiring more or less than 4 weeks of respiratory support at birth (figure e-1 on the Neurology® Web site at Neurology.org).

### Table 1: Demographic data

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Participants with congenital myotonic dystrophy ($n = 41$)</th>
<th>Control participants ($n = 29$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (SD)</td>
<td>6.8 (3.3)</td>
<td>9.1 (3.1)</td>
</tr>
<tr>
<td>Participants in cohort 1, aged 0-2 y, n</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Participants in cohort 2, aged 3-6 y, n</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>Participants in cohort 3, aged 7-13 y, n</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Female, %</td>
<td>49</td>
<td>59</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td>12 Hispanic, 88 non-Hispanic</td>
<td>7 Hispanic, 93 non-Hispanic</td>
</tr>
<tr>
<td>Race, %</td>
<td>98 Caucasian, 2 Asian</td>
<td>100 Caucasian</td>
</tr>
<tr>
<td>Mean CTG repeat length (SD)</td>
<td>1,245.97 (474.91)</td>
<td>NA</td>
</tr>
<tr>
<td>Mean duration of respiratory support at birth, wk (range)</td>
<td>25.9 [1-156]</td>
<td>0</td>
</tr>
<tr>
<td>Current respiratory support, % (mean duration of use during day)</td>
<td>7.0 BiPAP (13.3 h), 7.0 supplemental oxygen (9.6 h)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: BiPAP = bilevel positive airway pressure; NA = not applicable.

Oral facial strength testing. Children with CDM ($n = 23$) had a reduction in lip strength (2.1 N [SD 2.8]) compared to healthy controls (17.8 N [SD 7.6]) ($p < 0.001$). There was also a reduction in tongue strength in children with CDM (11.5 kPa [SD 7.8]) compared to healthy controls (41.8 kPa [SD 12.6]) ($p < 0.001$) as measured by the Iowa Oral Performance Instrument. In addition, children with CDM did not have the same improvement with age as healthy controls (figure 2, A and B). There was no association with CTG repeat length and lip or tongue force.
children with CDM able to perform the FVC testing was 11.1 years. The FVC range for children with CDM was 1.08 to 1.95 L. The mean FVC for children with CDM was 1.47 L.

Gastrointestinal testing. Of the 41 children with CDM, 30% were on a motility agent. The percentage of children with CDM who endorsed stomach pain was 9.7%, and 2 of 4 children who did endorse stomach pain reported that it was associated with meals. Of the 28 children older than 4 years, 39.3% had fecal incontinence.

We sought to understand the relationships among cognitive, oral facial, and strength and mobility difficulties (table 2). IQ did not correlate with the functional outcome measures. The measures of strength, mobility, and oral facial strength did correlate with each other ($p < 0.0001$).

**DISCUSSION** In this study, we were able to apply a series of frequently used clinical-oriented outcome measures to demonstrate the significant and multisystemic disease burden of CDM in childhood. We demonstrate the global impairment seen in children with CDM including differences in physical function, cognitive function, and quality of life compared to healthy...
controls. While intellectual impairment and oral facial weakness have been previously reported, this study further evaluates the disease burden associated with CDM. Specifically, we provide evidence of daytime sleepiness and motor delay that have not been previously reported. The outcome measures used in the study were chosen based on past pilot studies by the authors, recent patient-reported disease burden, and relevant literature focusing on CDM and other pediatric neuromuscular disorders. Feasibility and relevancy of certain measurements were based on age, and while a small proportion of children could not complete all measures, the feasibility was generally very good.

To date, few studies have tried to dissect the complex nature of CDM. Being rigorous in objectifying disease outcome measures, as we have done in this study, is so critical for several reasons. First, CDM is a complex dynamic disorder with indices of disease severity in childhood likely related to age in a bimodal pattern, trinucleotide repeat size, and severity of disease at birth. Second, the multisystemic nature of the disorder forces investigators to measure outcomes in a multiple system domain to understand the interrelationship and effect of each on the others. Finally, as we move closer to clinical trials, there is a pressing need for having feasible outcome measures that discern this population from normal controls and are responsive to change.

Consistent with our clinical impression, we did not observe poorer motor function with age, and in fact, some areas such as grip strength and 6MWD improved with time. Similarly, measures of oral facial strength were not worse with age. It is possible that a decline in motor function occurs at a later age.

IQ in this study did not vary with age. It is possible that aspects of CDM are neurodevelopmental and will remain static with development. This result will require validation with a longitudinal study, which we are currently conducting with the current cross-sectional sample reported here. When separating cohorts of larger CTG repeat expansions from smaller CTG repeat expansions, there was no evidence of a predictive value on function, with the exception of daytime sleepiness. Of note, children with CDM are distinct from adults with DM1, particularly given the improvement on a number of outcome measures during their childhood. This underscores the need to develop a distinct set of outcome measures for children with CDM.

The detection of cardiac arrhythmias in childhood underscores the importance of regular monitoring at any age. This reinforces a prior survey study reporting a prevalence of 24.1% of cardiac arrhythmias in childhood. Routine ECGs in childhood should be part of routine care.

Respiratory failure is frequently seen in the neonatal period of CDM, as previously reported. We note that respiratory function universally improved in our cohort, with no child requiring ventilation later in life. Several children required persistent nighttime respiratory assistance, suggesting that pulmonary function may not be completely normal. The measurement of FVC in this population was limited in this study, and additional work will be required to understand the relationship between CDM and respiratory function.

The frequent use of motility agents in children with CDM suggests that aggressive management of gastrointestinal symptoms is necessary in children. There was a significant range of bowel regimens used, and future studies may consider evaluating the relative effectiveness of such a diverse set of medications.

This study also provides a feasibility assessment of potential outcome measures in therapeutic studies. We note the relative consistency across all measures as evidence of feasibility, with the

Figure 2
Oral facial strength in CDM

(A) Lip force strength comparison between children with CDM and healthy controls. (B) Tongue strength comparison between children with CDM and healthy controls. CDM = congenital myotonic dystrophy.
exception of IQ. Appropriate age selection of children with CDM may prove difficult, as there is not a perceptible decline with age, at least in a cross-sectional analysis. However, the discriminant nature of many of the measures compared to controls is important in understanding the potential for responsiveness to change. An ongoing longitudinal study will assist in refining the course of CDM throughout childhood.

Finally, this study emphasizes the significant and multifaceted disease burden in CDM. Specifically, participants demonstrated differences in measures of intelligence, quality of life, and sleep in CDM. (A) IQ by age in children with CDM. (B) IQ by age, separating high and low CTG repeat expansions. (C) Daytime sleepiness by age in children with CDM. (D) Daytime sleepiness by age, separating high and low CTG repeat expansions. (E) Pediatric sleep quality in children with CDM. (F) Pediatric sleep quality by age, separating high and low CTG repeat expansions. (G) Pediatric quality of life in children with CDM and in healthy controls. (H) Pediatric quality of life in children with high or low CTG repeat expansions. CDM = congenital myotonic dystrophy; PDSS = Pediatric Daytime Sleepiness Scale; PedsQL = Pediatric Quality of Life Inventory; PSQ = Pediatric Sleep Questionnaire.
cognitive, physical, gastrointestinal, and cardiac function. Clinical care should reflect this need for comprehensive care and requires a multidisciplinary care approach.

There are limitations to this study. Few participants lived in the geographic region of the centers. Many of the participants traveled to the center, and therefore may have had more resources to participate in our study than patients without the ability to travel. Because of enrollment, the youngest healthy control that was able to participate in functional measurements (excluding those controls in the youngest cohort) was age 5, which limited the ability to fully compare the youngest participants with CDM. The measurements of CTG repeat length were obtained from clinical genetic testing, which was not conducted during the study visit. Therefore, it is possible there are minor changes in the CTG repeat length measurement. Cardiac assessments were limited to an ECG and did not include echocardiography or Holter monitoring. Therefore, the description is limited to ECG data. This is a cross-sectional study, so description of disease progression is limited to a between-participant comparison.

Overall, children with CDM have differences in speech, cognition, and motor function as compared to healthy children. Nearly all of these differences do improve with age. This may suggest that the initial perinatal difficulties are primarily a neurodevelopmental problem, or that ongoing disease processes in children may be mitigated with growth and development.

**AUTHOR CONTRIBUTIONS**

Nicholas E. Johnson: design of study, analysis of data, drafting of manuscript. Russell Butterfield: analysis of data, revision of manuscript. Kiera Berggren: design of study, analysis of data, revision of manuscript. Wei Chen: analysis of data, revision of manuscript. Deanna DiBella: design of study, analysis of data, revision of manuscript. Melissa Dixon: design of study, analysis of data, revision of manuscript. Heather Hayes: design of study, analysis of data, revision of manuscript. Evan Pucillo: design of study, analysis of data, revision of manuscript. Craig Campbell: design of study, analysis of data, revision of manuscript. Man Hung: analysis of data, revision of manuscript. Craig Campbell: analysis of data, revision of manuscript. Deanna DiBella: design of study, analysis of data, revision of manuscript. Russell Butterfield: analysis of data, revision of manuscript. Vivian Chen: analysis of data, revision of manuscript. Go to Neurology.org for full disclosures.

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