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Physical Function and Mobility in Children with Congenital Myotonic Dystrophy

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Abstract

Introduction—Congenital Myotonic Dystrophy (CDM) occurs when symptoms of myotonic dystrophy present at birth. This study evaluated the relationship between physical function, muscle mass, and age to provide an assessment of the disease and help prepare for therapeutic trials.

Methods—CDM participants performed timed functional tests (TFTs). The first 2 minutes of the 6-minute walk test (2/6MWT), myometry, and dual-energy x-ray absorption (DEXA) scans. Healthy controls (HC) performed TFTs, 6MWT, and myometry.

Results—Thirty-seven children with CDM and 27 HC, ages 3-13, participated. There were significant differences in the 10-meter walk (11.3s in CDM vs 6.8s in HC) and 2MWT (91m in CDM vs 193m in HC). DEXA lean mass of the right arm correlated with grip strength ($r=0.91$), and lean mass of right leg with 6MWT ($r=0.62$).

Conclusion—Children with CDM have significant limitations in strength and mobility. The tests performed were reliable, and lean muscle mass may serve as a useful biomarker.

Keywords

Myotonic Dystrophy; Functional Outcomes; Congenital Myotonic Dystrophy; Mobility Measures; Six-Minute Walk Test

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Introduction

Myotonic Dystrophy (DM1) is the result of a trinucleotide CTG_n repeat expansion in the 3' untranslated region of the *DMPK* gene.¹⁻⁴ This CTG repeat can rapidly expand between generations, particularly when the mother is affected. Significant repeat expansions may lead to symptoms at birth, known as congenital myotonic dystrophy (CDM).^{5,6}

Children with CDM have high mortality in the newborn period and display significant impairments in physical function throughout childhood.⁷⁻¹⁶ Clinical features in children with CDM include hypotonia, weakness, feeding difficulties, cognitive impairment, and respiratory failure requiring intubation and ventilation immediately after birth.^{8,10,14,16-19}

A prior cross-sectional study has identified hand weakness and difficulty with ambulation as affecting quality of life in CDM.^{20,21} Despite this, little data have been collected for functional outcome measures in CDM.^{22,23} One study attempted to measure isometric muscle strength using handheld myometry in children with CDM.²² However, the investigators were unable to collect sufficient data due to the participants having difficulty following directions.²² Another study measured timed function tests, manual muscle tests, and pulmonary function tests in 17 individuals with CDM over age 10 years.²⁴ Physical ability in children with CDM had been measured previously using the Motor Function Measure (MFM)²⁵ and a similar motor function scale.²² However, prior studies were limited by sample size, age restriction, and a smaller subset of functional measures.^{22,23}

In this study we aimed to comprehensively evaluate available outcome measures for use in therapeutic trials. Accordingly, the study goals were to: 1) compare TFTs for healthy controls (HC) and children with CDM; 2) determine the feasibility, reliability, and agreement of functional measures; 3) determine any relationships between dual-energy x-ray absorption (DEXA) lean mass and functional measures for children with CDM.

Materials and Methods

Participants with CDM between ages 3 and 13 years were enrolled at the University of Utah (n=34) and the University of Western Ontario, Canada (n=3). The Institutional Review Boards at both institutions approved all study procedures and informed consent was obtained. Participants were included if they met the research definition for CDM and had no other major medical illnesses.²⁰ CDM was defined as the following: 1) symptoms present at birth; 2) newborn symptoms including hypotonia, feeding difficulties, talipes equinovarus, or respiratory failure; and 3) confirmed genetic testing revealing a CTG repeat in the *DMPK* gene greater than 200 repeats. Subjects were excluded if they had any non-DM1 illness that would interfere with their ability to complete study procedures. HC (n=27) between ages 3 and 13 years were included if they had no major medical problems and were not currently on any medications.

Timed Functional Testing

Timed function tests (TFTs) were performed in accordance with previous pediatric studies of neuromuscular disorders.^{22,23,26-28} Timed activities included: time to climb 4 stairs

(4SC), time to rise from the floor starting in a supine position, 10-meter run, and 10-meter self-selected walking speed. A stopwatch was used, and participants were given a maximum of 60 seconds to complete all tasks. If a subject was unable to complete the task, the time was not recorded. Correlations were analyzed for children with CDM between TFTs and age, and also for TFTs and number of CTG_n repeats.

6MWT and 2MWT

The 6MWT was conducted in HCs and children with CDM along a 25-meter course using criteria cited in previous studies.²⁶⁻²⁸ The time at 2 minutes was recorded during the 6MWT and was referred to as the 2MWT. Orthotics and assistive devices for ambulation were allowed. Continuous verbal encouragement was given from the evaluators and parents during the test to ensure the subjects remained attentive. The 6MWT was performed over 2 consecutive days in children with CDM for reliability testing. HCs performed the walk test on a single day. Subjects who were physically unable to walk were given a distance of 0m for the 6MWT and 2MWT.

Grip and Pinch Myometry

The average of 3 trials of grip and pinch measurements for maximum voluntary isometric contraction (MVIC) was collected from both hands in HC and children with CDM. Handgrip was collected using the JAMAR Plus+ digital hand dynamometer (*Sammons Preston*). Jaw chuck pinch and lateral pinch were collected using the JAMAR Plus+ digital pinch gauge (*Sammons Preston*). Participants were instructed to grip and pinch as hard as they were able with the hand and forearm resting at their sides in 90 degrees of elbow flexion and neutral pronation/supination.

Handheld Myometry

Strength testing was collected in HCs and children with CDM ages 4-13 on 4 muscle groups, bilateral shoulder abductors and ankle dorsiflexors using a Commander Muscle Tester (*PowerTrack II, JTECH medical*). A make test was conducted. Shoulder abduction was collected with the patient in the seated position with the shoulder abducted to 90 degrees and the elbow flexed a few degrees with a dynamometer placed proximal to the lateral humeral epicondyles. Ankle dorsiflexion was tested in the seated position with the legs flexed over the edge of the table with shoes off, lower leg stabilized above the ankle joint, and the myometer placed on the dorsum of the foot over the metatarsals. Dorsiflexion with inversion was allowed, as many children with CDM had difficulty isolating pure dorsiflexion. Three trials were collected per muscle, and the average was recorded.

Dual-Energy X-ray Absorption (DEXA)

Whole-body DEXA scans were performed on children with CDM using a Hologic Discovery machine running Apex version 3.2 software. HCs did not undergo DEXA scans. Children were positioned according to manufacturer recommendations and when cooperation could not be solicited from a few of the children on occasion, a cotton sheet was used to swaddle the child to minimize movement artifact. Scans of the lean mass of the right

arm and leg were acquired and analyzed by a licensed and certified technician by the International Society for Clinical Densitometry.

Bruininks-Oseretsky Test of Motor Proficiency – 2nd edition (BOT-2)

The BOT-2 fine motor control and manual coordination subtests were attempted in 25 of the children with CDM between ages 4 and 13. Each subject's percentile rank was calculated in relation to the previously established standardized and norm-referenced values.²⁹

Statistical Analysis

Independent samples *t*-tests or Wilcoxon 2-sample tests were used to compare the differences in functional measures between CDM and the control group. Pearson correlation was performed to determine the relationship between the upper and lower extremity outcome measures and the DEXA lean mass. Intra-class correlation (ICC) and Bland-Altman analyses were used to test the reliability between Days 1 and 2 of the 6MWT and 2MWT. Family-wise error was corrected for by using Holm-Bonferroni methods. All analyses were conducted using SAS 9.4 statistical software, and *P*-values <0.05 were considered significant.

Results

Participant Demographics

The study enrolled 37 participants with CDM and 27 healthy controls (HC). Detailed demographic data including age, gender, ethnicity, race, and CTG_n repeat number are provided in Table 1.

Timed Function Test

When comparing TFTs, children with CDM performed significantly lower than HC in all 4 measures (4SC, 10m walk, 10m run, time to rise from floor) after adjusting for age. The mean $\pm$ SD for the 10m walk for CDM (N=31) was 11.3 $\pm$ 6.9 sec, while for HCs (N=26) it was 6.8 $\pm$ 1.8 sec (*P*<0.001). The mean $\pm$ SD for the 10m run for CDM (N=29) was 6.1 $\pm$ 3.1 sec, while for HCs (N=25) it was 3.2 $\pm$ 0.5 sec (*P*<0.001). The mean $\pm$ SD for time to rise from the floor for CDM (N=26) was 9.4 $\pm$ 6.3 sec, while for HCs (N=25) it was 2.0 $\pm$ 0.6 sec (*P*<0.001). The mean $\pm$ SD for the 4SC for CDM (N=29) was 7.0 $\pm$ 7.6 sec, while for HCs (N=26) it was 1.5 $\pm$ 0.3 sec (*P*<0.001).

Some participants with CDM were unable to complete the test for physical, behavioral, or cognitive reasons. Behavioral difficulties included participants with CDM being easily distractible, uncooperative, or sometimes refusing to perform the tests. A time was recorded only if the participant was able to complete the test. The percentage of participants with CDM who were scored for the TFTs are the following: 10 m walk (83.8%), 10m run (78.4%), 4SC (78.4%), and time to rise from floor (74%). Analysis of TFT results versus age as a function of CTG_n repeat length (> or < 1000) in children with CDM can be found in Supplementary Figure S1, available online.

6MWT and 2MWT

The total 6MWT distance has been previously reported.³⁰ Behavioral difficulties prevented some participants (11%) from completing the full 6MWT, but all participants were able to complete at least the first 2 minutes. Similar to the 6MWT, 2MWT results were significantly different in the CDM population [CDM: 91m $\pm$ 58.9 vs. HC: 193m $\pm$ 22.7 ($P < 0.0001$)] as seen in Figure 1. Both walk tests had high test-retest reliability (2MWT ICC=0.94; 6MWT ICC=0.96). Bland-Altman plots of test-retest reliability can be found in Figure 2. For the 6MWT, the mean difference between days 1 and 2 is close to 0, 1.46m/min or 8.52m over 6 minutes, and thereby indicates our 6MWT has test-retest reliability. Likewise for the 2MWT, the mean difference between days 1 and 2 was 0.66m/min or 1.32m over 2 minutes. The 2MWT overall has a smaller mean difference than 6MWT. No systematic change was noted, as the Bland-Altman plot shows random changes in the mean values between the 2 test occasions.

Correlation of TFTs and Walk Tests

The first 2 minutes of the 6MWT and the 2MWT correlated highly with each other (Table 2). Gait speed items, 10m run and 4SC, and 10m run and 10m walk had strong correlations. Modest correlations were found between all other comparisons (Table 2).

Handheld Myometry

Results are reported in Supplementary Table S1, available online. The average ages of children with CDM able to complete shoulder abduction myometry was 9.51 years and 9.98 years for ankle dorsiflexion myometry.

DEXA

DEXA lean mass results by age and gender for children with CDM ($n=29$) are found in Supplementary Figure 2. The mean DEXA total lean mass for males (15,058 g/cm²) is higher than females (13,013 g/cm²), but the difference is not significant ($P=0.539$). The total lean mass correlates significantly with age for children with CDM ($r=0.808$, $P<0.001$). DEXA lean mass of the right arm correlated well with all 3 measures of hand strength (Table 3). However, when comparing DEXA lean mass of the lower extremity and total lean body mass with 10m walk or 2MWT/6MWT performances, only modest correlations were found for each measure (2MWT $r=0.59$, 6MWT $r=0.62$, 10m walk $r=-0.38$) (Tables 2 and 3).

Exploratory measures

The BOT-2 assesses fine motor control and manual dexterity. It was administered to 25 children with CDM between ages 4 and 13 (average age 8.1 years). Ninety-four percent of participants scored in the 0 to second percentile when compared to norm-referenced values for fine motor control, manual coordination, and fine motor composite. One subject scored in the eighth percentile for fine manual control. Seventy-two percent of children with CDM were able to complete the fine manual control and manual coordination subsets of the BOT-2.

Discussion

This study provides a cross-sectional understanding of physical function in children with CDM. There is evidence that strength improves throughout childhood, albeit at different rates depending on the outcome measure used. However, despite improvement, the children with CDM who were evaluated remained lower than their healthy peers. In general, the improvement between age groups on the measures assessed stands in contrast to those studies in adults with DM1, where strength declines over time.^{31,32} It is possible that CDM represents a developmental disorder, and that natural muscle maturation may partially compensate for the underlying pathophysiology. Future studies should attempt to compare individuals of adult-aged CDM with adults with DM1, and likewise children with CDM to those individuals with childhood onset DM1.

This study was designed to prepare for clinical trials in children with CDM by evaluating the feasibility, reliability, and validity of functional outcome measures. Overall, the measures assessed met criteria for inclusion in clinical trials in that they were reliable and generally completed. The 6MWT and 2MWT were found to have excellent test-retest reliability. It appears that children with CDM have decreased performance on TFTs if they possess >1,000 CTG_n repeats when compared to their peers with CDM who have <1,000 CTG_n repeats (Supplementary Figure S1, available online). DEXA lean body mass may be an effective clinical tool to utilize in future studies for predicting functional upper extremity strength and may be a potential biomarker to monitor functional changes in disease progression.

Given the association of intellectual impairment in children with CDM, functional outcomes may have variable completion rates.^{9,21,33,34,24} The TFTs and 6MWT described above had acceptable rates of completion. Future studies may consider using the 2MWT rather than the 6MWT, because more children were able to complete the first 2 minutes of the 6MWT than the full 6MWT. Tests with lowest completion rates for children with CDM included spirometry, BOT-2, and myometry of the ankle dorsiflexors. We also found that children with CDM displayed a floor effect on the BOT-2, whereby no subjects who were able to complete the test had scored above the eighth percentile on any of the subtests of fine manual control and manual coordination.

There are limitations to this study. First, the study is cross-sectional in nature. Future longitudinal studies will be required to obtain within-participant comparisons. Secondly, many of our participants were remote from the study center and required travel, which may have contributed to fatigue. Thirdly, intellectual impairment and behavioral problems in some children with CDM limited the completion rate of some tests. Finally, the first 2 minutes of the 6MWT were used rather than a separate 2MWT. Future results may vary with the use of the actual 2MWT as a stand-alone measure.

Overall, this study defines some of the limitations of physical function during childhood in children with CDM. Due to the nature of CDM, there was a degree of variability between each subject's ability to complete the full battery of physical function assessments. Children with CDM may display autistic-like characteristics.^{9,21} Despite these obstacles this study

showed that most children with CDM were able to complete the walk tests, TFTs, and DEXA scans. Future studies should continue to examine and seek to validate various measures of functional mobility in children with CDM to better understand disease progression and prepare for clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Butterfield serves on the scientific advisory boards for Bamboo Therapeutics, Sarepta Therapeutics, Marathon Pharmaceuticals, and Avexis. He is the site principal investigator for clinical trials sponsored by Marathon Pharmaceuticals, Sarepta Therapeutics, Pfizer, Eli Lilly, PTC Therapeutics, and aTyr Pharma.

Dr. Campbell is on advisory boards for PTC Therapeutics and voluntary consultative meetings for Biomarin and Acceleron. He is a site PI for clinical trials sponsored by Biogen, Ionis, PTC Therapeutics, Eli Lilly, and Pfizer.

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Abbreviations

2MWT	Two-minute walk test
6MWT	Six-minute walk test
4SC	Four-stair climb
AD	Ankle Dorsiflexors
BOT-2	Bruininks-Oseretsky
CDM	Congenital Myotonic Dystrophy
DEXA	Dual-energy X-ray absorption
DM1	Myotonic Dystrophy Type 1
HC	Healthy Control
HHD	Handheld dynamometry
MFM	Motor Function Measure
MVIC	Maximum Voluntary Isometric Contraction
SA	Shoulder Abductors
TFTs	Timed Function Tests

Figure 1. Comparison of TFTs for CDM and HC by age

(The 2MWT day 1 and day 2 measurements are within the 95% limits of agreement and thus they may be used interchangeably. Most of the measurement points for the 6MWT day 1 and day 2 are also within the 95% limits of agreement.)

Figure 2. Bland-Altman graphs of 2MWT and 6MWT test-retest reliability

Table 1**Participant Demographics**

Variable	CDM	Control
Number	37	27
Age mean ($\pm$ SD) yrs.	7.4 ($\pm$ 3.0)	9.7 ($\pm$ 2.3)
Age range yrs.	3 -13.2	5.6 – 13.9
CTG _n repeats ($\pm$ SD) (N=30)	1226.9 ($\pm$ 462.6)	Not tested
Range of CTG _n repeats (N=30)	400-2,530	Not tested
Gender		
Male N (%)	18 (49%)	12 (44%)
Female N (%)	19 (51%)	15 (56%)
Ethnicity		
Hispanic N (%)	3 (8%)	2 (7%)
Not Hispanic N (%)	34 (92%)	25 (93%)
Race		
Asian N (%)	1 (3%)	0
White N (%)	36 (97%)	27 (100%)

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Table 2

Pearson coefficients for walk tests and TFTs

MEASURE	DEXA Total Lean Mass	2MWT	6MWT	10m walk	4 Stair climb	Rise from floor	10m run
DEXA Total Lean Mass	1.00						
2MWT	0.62 $P=0.001$	1.00					
6MWT	0.62 $P=0.001$	0.98 $P<0.0001$	1.00				
10m walk	-0.39 $P=0.066$	-0.72 $P<0.0001$	-0.76 $P<0.0001$	1.00			
4 Stair climb	-0.44 $P=0.043$	-0.56 $P=0.0016$	-0.60 $P=0.0012$	0.73 $P<0.0001$	1.00		
Rise from floor	-0.28 $P=0.239$	-0.66 $P=0.0003$	-0.66 $P=0.0006$	0.57 $P=0.0025$	0.55 $P=0.0042$	1.00	
10m run	-0.54 $P=0.012$	-0.71 $P<0.0001$	-0.78 $P<0.0001$	0.82 $P<0.0001$	0.85 $P<0.0001$	0.67 $P=0.0003$	1.00

Table 3
Pearson correlation for DEXA results compared with functional tests

MEASURE	Total body lean mass	Lean mass of the right arm	Right grip	Right pinch	Right jaw chuck
Total body lean mass	1.00				
Lean mass of the right arm		1.00			
Right grip	0.84 $P<0.001$	0.91 $P<0.0001$	1.00		
Right lateral pinch	0.76 $P<0.001$	0.83 $P<0.0001$	0.94 $P<0.0001$	1.00	
Right jaw chuck	0.73 $P<0.001$	0.77 $P=0.0009$	0.86 $P<0.0001$	0.78 $P<0.0001$	1.00
MEASURE	Total body lean mass	Lean mass of the right leg	2MWT	6MWT	10m walk
Total body lean mass	1.00				
Lean mass of the right leg		1.00			
2MWT	0.62 $P=0.001$	0.59 $P=0.0047$	1.00		
6MWT	0.62 $P=0.001$	0.62 $P=0.0034$	0.98 $P<0.0001$	1.00	
10m walk*	-0.39 $P=0.066$	-0.38 $P=0.1345$	-0.73 $P<0.0001$	-0.76 $P<0.0001$	1.00

* An inverse correlation is found between lean mass of the right leg and 10m walk, as increasing lean mass should result in less time to complete the 10m walk.