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Kellen H. Quigg
Virginia Commonwealth University

Kiera N. Berggren
Virginia Commonwealth University

Melissa McIntyre
The University of Utah

Kameron Bates
Virginia Commonwealth University

Francesca Salmin
NEuroMuscular Omnicentre (NEMO)

See next page for additional authors

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12-Month Progression of Motor and Functional Outcomes in Congenital Myotonic Dystrophy

Kellen H Quigg, MD[1], **Kiera N Berggren, MA/CCC-SLP, MS**[1], **Melissa McIntyre, DPT**[2], **Kameron Bates, MS**[1], **Francesca Salmin, PT**[3], **Jacopo L. Casiraghi, PsyD**[3], **Adele D'Amico, MD**[4], **Guja Astrea, MD**[5], **Federica Ricci, MD**[6], **Marnee J. McKay, PhD**[7], **Jennifer N. Baldwin, PhD**[8], **Joshua Burns, PhD**[7], **Craig Campbell, MD**[9], **Valeria A Sansone, MD**[3], **Nicholas E Johnson, MD**[1]

[1.] Virginia Commonwealth University Health, Department of Neurology, Richmond, VA, USA

[2.] University of Utah, Department of Pediatric Neurology, Salt Lake City, Utah, USA

[3.] The NEuroMuscular Omnicentre (NEMO) Clinical Center, Milan, Italy

[4.] Bambino Gesù Children's Hospital, Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, Rome, Italy

[5.] Scientific Institute for Research Hospitalization and Health Care (IRCCS) Stella Maris, Department of Developmental Neuroscience, Pisa, Italy

[6.] Regina Margherita Children's Hospital, Department of Pediatrics, Section of Child and Adolescent Neuropsychiatry, Turin, Italy

[7.] The University of Sydney, Faculty of Medicine and Health, Sydney School of Health Sciences, Sydney, Australia

[8.] Priority Research Centre for Physical Activity and Nutrition, The University of Newcastle, Callaghan, Australia

[9.] London Children's Hospital, University of Western Ontario, Department of Pediatrics, London, Ontario, Canada

Abstract

Introduction/Aims: We aim to describe 12-month functional and motor outcome performance in a cohort of participants with congenital myotonic dystrophy (CDM).

Methods: CDM participants performed the Six Minute Walk Test (6MWT), 10 Meter Run, 4 Stair Climb, Grip Strength and Lip Force at baseline and 12 month visits. Parents completed the Vineland Adaptive Behavior Scale.

Results: Forty-seven participants, aged 0 to 13 years old, with CDM were enrolled. 6MWT, 10 Meter Run and 4 Stair Climb were completed in >85% of eligible participants. The only

Corresponding Author: Nicholas Johnson, MD, 1101 East Marshall St, PO Box 980599, Richmond, VA, 23298, Nicholas.johnson@vcuhealth.org.

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significant difference between mean baseline and 12-month performance was an improvement in 6MWT in children 3–6 years old (p=0.008). This age group also had the largest mean % improvement in performance in all other timed functional testing. In children >7 years, the slope of change on timed functional tests decreased or plateaued, with further reductions in performance in children ≥10 years. Participants with CTG repeat lengths <500 did not perform differently than those with repeat lengths >1000.

Discussion: 6MWT, 10 Meter Run and 4 Stair Climb were the most feasible measures. Our findings are consistent with the clinical profile and prior cross-sectional data, helping to establish reasonable expectations of functional trajectories in this population as well as identifying points in which therapeutic interventions may be best studied. Further study of outcomes in children >10 years old and <3 years is warranted, but this new information will assist planning of clinical trials in the CDM population.

Keywords

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

Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disease caused by a CTG_n trinucleotide repeat expansion in the 3'UTR of the *DMPK* gene.[1–3] The repeat length may expand dramatically between generations, particularly when inherited through the mother, known as anticipation.[4] Large repeat expansions are associated with symptoms at birth, known as congenital myotonic dystrophy (CDM),[5] although there is no single repeat length which alone predicts timing of symptom onset.

CDM represents the most severe form of the disease and is characterized by hypotonia, feeding difficulties and respiratory distress at birth.[6] Children with CDM experience weakness and cognitive impairment, with delayed motor milestones and behavioral difficulties.[6–8] Muscle strength improves in early childhood, with behavioral and cognitive impairments becoming the predominant symptoms.[9, 10] Eventually symptoms are more consistent with adult DM1, without correlation to severity of neonatal symptoms.[11] The timing, rates of change, and points of inflection towards adult DM1 phenotypes are unknown.

Given the severity of the disease and complex pathophysiology, CDM is an appealing target for clinical trials with multiple opportunities for targeted therapeutics. Prior to trial development a better understanding of CDM disease progression, as well as feasibility and reliability of outcome measures, is needed. In this study, we aim to 1) describe 12-month progression of strength and functional outcomes in patients with CDM, 2) compare CDM outcomes to age-matched normative data, 3) evaluate feasibility of measuring fine motor and gross motor outcomes in a cohort of CDM patients <3 years old as measured via the Vineland Adaptive Behavior Scale (VABS).

Methods

Study Design and Patients

Patients with CDM ages 0–13 years, 11 months old were enrolled in a prospective, longitudinal, multi-center observational study at the University of Utah, the University of Western Ontario, Canada, and the NEuroMuscular Omnicentre (NEMO) in Milan, Italy. Diagnosis of CDM was defined as symptoms of myotonic dystrophy in the newborn period (<30 days) including hypotonia, respiratory distress, feeding difficulty, or talipes equinovarus, requiring hospitalization greater than 72 hours, and a genetic test confirming an expanded trinucleotide (CTG) repeat in the *DMPK* gene in the child or an affected mother. An expanded CTG repeat size of greater than 200 repeats in the child was considered confirmatory for CDM. Participants were excluded if they experienced any other illness that would interfere with study results as determined by site investigators.

Written informed consent was obtained from one parent and verbal assent from children over the age of 8. Institutional Review Boards approved all study procedures prior to enrollment of participants at each site.

Normative data was provided by the 1000 Norms Project, [12–14] an observational study investigating outcome measures of self-reported health and physical function in 1000 healthy individuals aged 3 to 101 years.

Procedures

For all outcomes, evaluators underwent standardized training, including demonstration of competency with certified experts. Given pronounced cognitive delays and difficulty with attention in many CDM patients, sites were permitted to make exceptions to the administration of testing. For participants unable to follow protocoled instructions after one trial, aids such as light contact cueing, parent and evaluator encouragement, and provision of items of interest during the tasks as motivation were allowed.

Functional Motor Testing—Six Minute Walk Testing (6MWT) was performed in accordance with previously validated protocols.[15, 16] Total distance walked, in meters, was recorded.

10 Meter Run and 4 Stair Climb were performed as previously documented.[17] A stopwatch was used to measure time in seconds. For the 4 Stair Climb, the end position with hands at side was often not fully obtained, thus the timer was stopped once the child was balanced with both feet at the top of the stairs.

Strength Testing—Grip strength was collected using the JAMAR Plus+ digital hand dynamometer (Sammons Preston, Warrenville, Illinois, USA). Dominant hand was identified according to parent report. Participants were instructed to squeeze as hard as possible with hand and forearm in neutral pronation/supination and elbow in 90 degrees of flexion. Three trials were attempted; the average of the trials is reported. Grip strength was measured in kilograms and converted to Newtons by standard conversion of 9.807. Normative data was collected in the same position, with maximal force exerted for 3–5 seconds. Results were

measured in Newtons using the Citec Hand Held Dynamometer (CT 3001, CIT Technics, Arnhem, Netherlands.)

Ankle dorsiflexion was collected using a Commander Muscle Tester (PowerTrack II, JTECH medical, Midvale, Utah, USA). Dorsiflexion strength was assessed with shoes off in the seated position with the leg flexed over the edge of the table. The evaluator manually stabilized the ankle joint and placed the myometer over the dorsum of the foot at the metatarsals. Dorsiflexion with inversion was permitted, due to the difficulty of CDM patients achieving pure dorsiflexion. Three trials were attempted; the average of the trials is reported. All measures were converted from kg to N using the aforementioned conversion.

Lip strength was measured using the Imada DS2 Digital Force Gauge (Imada, Inc., Northbrook, Illinois, USA) attached to a Vettex Doubleguard Mouthguard Pee Wee (Model PW22; Markwort Sporting Goods Co., St. Louis, Missouri, USA) as previously described.[18] Participants were seated in chairs in the position tin which testing was best tolerated. Use of the Lip Force Meter was first demonstrated by the clinical evaluator. The meter was then placed in the participant's mouth and they were instructed to hold it with their lips and resist the pulling force from the evaluator for as long as they could with closed lips. An average of three trials is reported.

Vineland Adaptive Behavior Scale—VABS[19] is an instrument evaluating a child's adaptive abilities relative to normally developing children. Subcategories of behaviors include communication (receptive, expressive, written), daily living skills (personal, domestic, community), socialization (interpersonal relationships, play and leisure, coping skills) and motor skills (gross motor and fine motor). Surveys were either provided to participants' parents for completion or were completed with assistance from a qualified assessor.

Scores on subdomains are represented as v-scores, calculated from primary norm-referenced values. V-scores of 1–9 indicate low adaptive levels, 10–12 moderately low, 13–17 adequate, 18–20 moderately high and 21–24 high. Average norm-referenced v-scores are 15±SD 3. The subdomain scores are compiled as an Adaptive Behavior Composite (ABC) score, which is then converted to a percentile rank as compared to age-matched normative samples.

Statistical Analysis

Comparisons between baseline and 12-month performance were assessed using paired *t*-tests. P-values <0.05 were considered significant. Analysis and descriptive statistics were performed using R statistical software version 3.6.2. Calculations for 6MWT percent of predicted performance as compared to age-matched healthy individuals were made using the Geiger equation.[20]

Results

Forty-eight participants with CDM were enrolled. One participant was excluded as he did not meet criteria. The participant had neonatal respiratory failure but after review of the clinical context it was not felt to be related to DM1. Data are presented by age group based

on age at baseline visit: <3 years, 3.0–6.99 years, 7.0–9.99 years and ≥ 10 years. The 1000 Norms Project provided normative data on 204 healthy children, with n=20 for each age 3–9 years and n=16 for each age 10–14 years. Gender, male/female, was equally represented in each age group.

Baseline characteristics are presented in Table 1. Repeat lengths were available for 40 of 47 participants. One repeat length was reported as 300+ and was thus assigned 300. Demographics and neonatal clinical characteristics of participants without known repeat lengths are displayed as part of supplementary materials (Table S1).

Of the participants with ECG abnormalities deemed clinically significant by study investigators, one had long PR and wide QRS intervals, two had right ventricular hypertrophy, one had an unspecified atrial arrhythmia with long PR interval, and one had tachycardia, T-wave abnormalities, right ventricular hypertrophy and long PR interval.

Feasibility assessments of functional outcomes in those who were able to walk independently and over the age of 3 years identified an 87% (26/30) completion of the 6MWT, 83% (25/30) of the 10 Meter Run, 93% (28/30) completion of the 4 Stair Climb ascent portion, and 87% (26/30) of the descent. Results marked invalid were primarily due to physical limitations. The feasibility of grip strength and lip force measurements was 64% (25/39) and 51% (20/39), respectively. Invalid results for strength testing were due to inability to understand directions. Valid ankle dorsiflexion data was only available for 7 participants, and thus is not displayed. There was no valid functional motor data available for participants less than 3 years of age.

Baseline to 12-month progression data and associated repeat length are shown in Figure 1. Mean time between baseline and 12-month visit was 392 days (range 339–536); 15 participants had visits outside of the protocol-defined visit window of 1 year plus or minus 30 days. The mean percent change of all other outcomes from baseline to 12 months is displayed in Table 2.

There was a statistically significant difference showing improvement between mean baseline and 12-month performance on the 6MWT in the participants aged 3–6 years old. Improvement in performance for the participants aged 7–9 years did not reach statistical significance. At baseline, CDM participants walked a mean percent predicted distance of 40.9% (3–6y), 52.6% (7–9y), and 62.6% (≥10y), respectively. At 12 months, mean group performance in children aged <10 years improved, with percent predicted walking distance of 57.3%, p=0.08 (3–6y) and 64.2% p=0.33 (7–9y); however, on average, children aged ≥10 years had a reduction in predicted distance walked (61.3%, p=0.9). CDM 6MWT performance as compared to age-matched control is displayed in Figure 2. CDM participants performed consistently below, or at the lower end of normal, as compared to healthy controls in the 6MWT, with performance declining away from the normal curve with increasing age.

In all other timed function tests, children aged 3–6 years had the greatest mean % improvements in performance (Table 2). This improvement was less for children aged 7–9 years, with a very slight worsening of mean performance in the 10 Meter Run. Children

aged ≥10 years had the smallest mean % change in performance in timed function tests with a worsening in mean performance in 10 Meter Run and 4 Stair Descent.

These patterns were not observed in grip strength or lip force (Table 2). Grip strength in CDM participants reasonably matched control performance in children aged 3–6 years (Figure 2). Performance separated away from normative data with increasing age, aside from two children aged ≥10 years who performed equally to healthy peers.

VABS Gross Motor and Fine Motor scores, and ABC scores by repeat length are available as part of supplementary materials (Figure S1). All participants scored below the 80th percentile of their age-predicted ABC score at both baseline and 12-month visits. Gross Motor and Fine Motor Subscales are displayed in Figure 3. One participant (age 6.5 at baseline) achieved a v-score of 18, or moderately high adaptive functioning, in the Gross Motor subscale at the 12-month visit (an improvement of 10 points from baseline). All other scores remained below the threshold of 'adequate' at both points of testing.

There were 5 participants under the age of 3 for whom data were available. Relative to baseline assessments, average ABC percentile rank decreased in children aged <3 years. Two of the five children aged <3 years had reductions in ABC score percentile ranks of at least 30%. The youngest child showed improvement of less than 5%. The other two displayed negligible change. None of the children aged <3 years improved in the Fine Motor Subscale between baseline and 12 months. All five children aged<3 years scored below 13 on the Gross Motor Subscale. Three of 5 had further decline in v-scores at 12 months.

Discussion

Longitudinal data on standardized motor outcome measures in children with CDM are not available. This study fills a significant knowledge gap by providing information on 12-month progression in strength, timed motor tests and behavioral outcomes in children with CDM. Overall, children with CDM perform worse than healthy children of the same age. When evaluated over the age of 10 years, the gap between children with CDM and those healthy controls widens. Our observations in the 6MWT, 10 Meter Run and 4 Stair Climb descent support the trend of improvement in function in younger years, followed by a plateau or decrease in rates of improvement, before a steady decline in participants greater than 10 years of age. This finding is consistent with clinical observations and previous studies.[9–11] Given that only one subgroup had significant change over 12 months, and only in the 6MWT, outcome assessments at intervals of 12 months or longer appears to be reasonable. More frequent assessments likely would not reveal significant changes.

Lip force and grip strength in CDM participants did not mimic this pattern, but were obscured by some CDM subjects performing notably better than peers. It is also worth noting that cognitive impairment influenced feasibility of these two measures more than the functional measures, an important consideration for future clinical trials.

Interestingly, participants with repeat lengths between 500–1000 did not perform differently than those with repeats >1000. Although repeat length is often considered as a disease severity marker, the correlation with many disease characteristics is weak and overall the

repeat size should not be used for prognosis. Continued analysis of progression into older age ranges merits further study.

Results from the VABS showed a considerable functional decline in composite score and both motor subscores for those aged less than 3 years, though our sample size was very small. VABS did not demonstrate reliable trends across any of the other age groups. This could be because the scale is parent-reported, or because it does not capture the complexity of CDM comorbidities. Other comprehensive tools considered for evaluation of our CDM population included the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2), though previous cross-sectional data[21] in a CDM population demonstrated such poor results on the BOT-2, that further use of this tool as a potential clinical trial outcome measure would be futile. It appears most likely that a different measure, encompassing multiple functional and behavioral domains specific to myotonic dystrophy, which can be reliably completed by parent proxy, is needed for better evaluation.

Several limitations should be noted, most importantly the difficulty in obtaining reliable outcomes from patients with physical, cognitive and behavioral impairments. Due to these challenges, it is unclear whether functional and motor testing outcomes are a reflection of true maximum physical effort, or a child's ability to understand and follow instructions. This could be overcome by controlling for cognitive function with either IQ or neuropsychological testing, though reliable data on cognitive measurement selection is not yet available in this population. Oral aversion, which is recognized clinically in CDM and many other congenital muscular dystrophies[22], though not directly assessed in this study, also contributes to difficulties in obtaining reliable measures of orofacial function and should be further evaluated as a limitation in future investigations.

Selecting outcomes appropriate for patients across age groups is also challenging, though the availability of normative data can help to distinguish changes in longitudinal CDM outcome measurements that would be expected to improve in parallel with childhood development, from the relative flattening of the slope compared to healthy controls demonstrated in our cohort. This separation from the normal development curve is distinct from other pediatric neuromuscular diseases in which there is a frank decline in performance.[23] Regardless, 12-month progression data does not paint the whole picture of CDM disease evolution and progression. More data, over a longer period of time, and in other CDM patient samples are needed to better characterize longitudinal trends in this patient population, as well as more detailed investigation into feasibility of functional outcomes as they directly relate to cognitive impairment.

For purposes of clinical trial design and enrollment, it would be reasonable to target children at the plateau point, or the start of the slope of decline, in order to measure clinically meaningful delay or halt of disease progression. Evaluation of outcomes at 12-month intervals is also a reasonable timeline for assessment in future trials. These data are foundational work in moving the field toward selecting the most feasible, reliable and valid outcome measures for clinical and research work. From this study, functional measures such as 6MWT, 10 Meter Run and 4 Stair Climb appear to be the most feasible and consistent with prior cross-sectional data. The CDM community needs progress in understanding

outcome measures beyond motor measures, such as patient reported outcomes and parent proxy questionnaires, as well as cognitive and disease severity biomarkers, in order to be fully ready for evaluating novel therapeutics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CDM	Congenital Myotonic Dystrophy
6MWT	Six Minute Walk Test

DM1	Myotonic Dystrophy Type 1
VABS	Vineland Adaptive Behavior Scale
ABC Score	Adaptive Behavior Composite Score
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency

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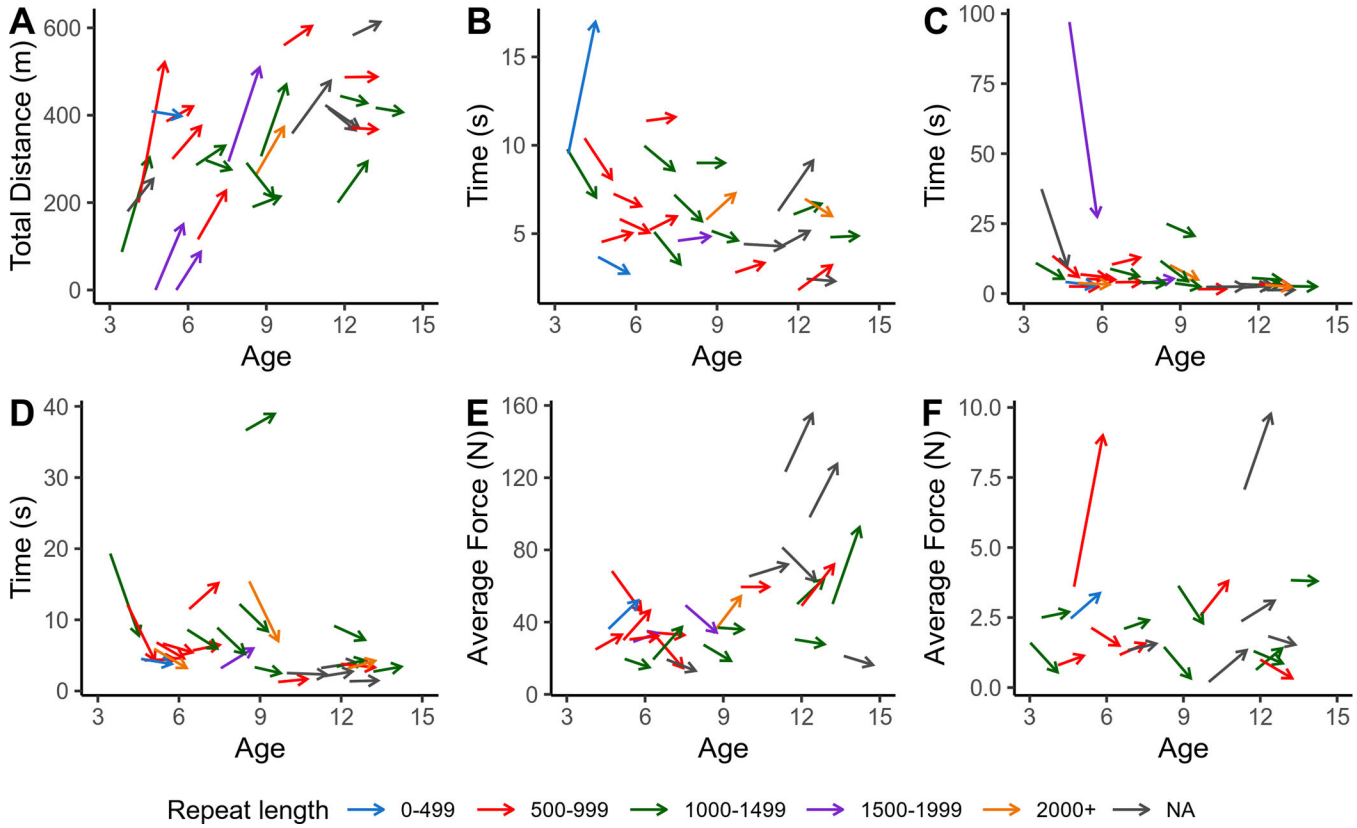

Figure 1: Baseline to 12 month Performance with Repeat Length.

A) 6 Minute Walk; B) 10 Meter Run; C) 4 Stair Climb-Ascent; D) 4 Stair Climb-Descent; E) Grip Strength; F) Lip Force. Arrows represent individual subject performance. Blunted end of arrow represents baseline performance. Arrow heads correspond with 12-month visit performance.

NA = Not Available; s = seconds; m = meters; N = Newtons.

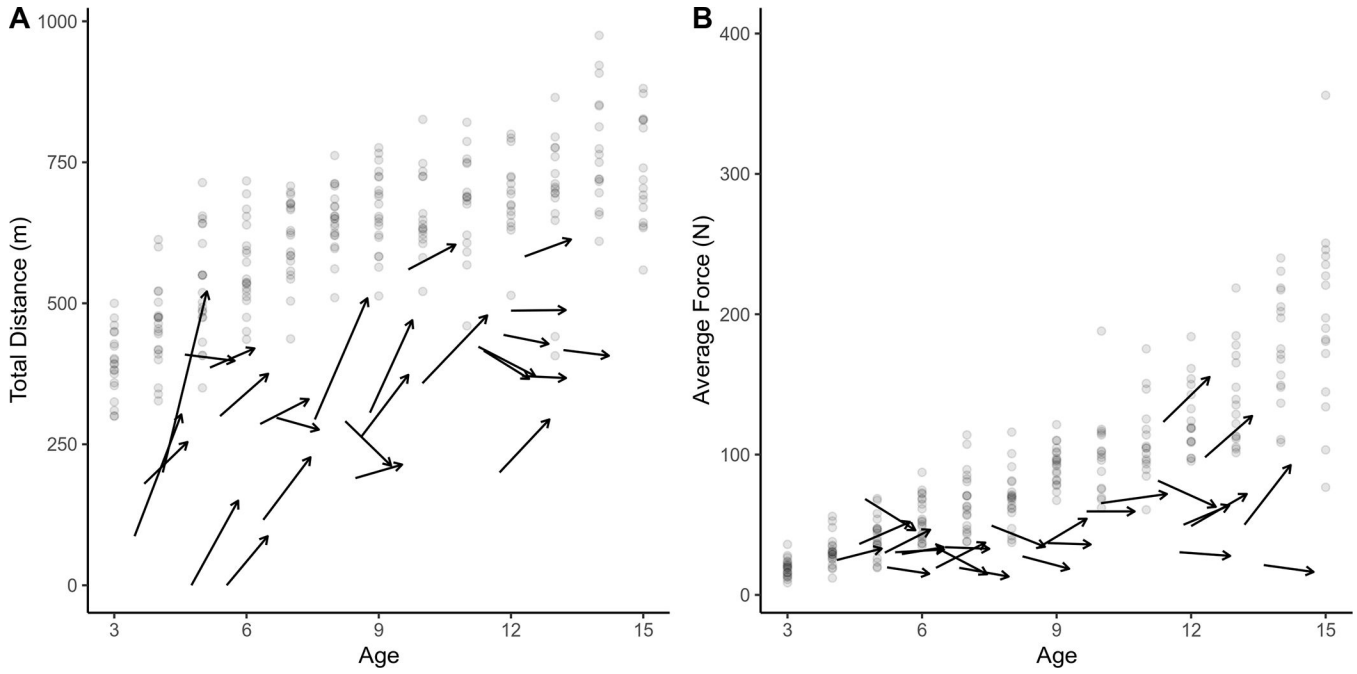

Figure 2: CDM Participant Performance Compared to Normal Controls.

A) 6 Minute Walk; B) Grip Strength.

Controls from the 1,000 Norms Study are represented by shaded circles. Increasing densities represent overlapping performance. Solid arrows represent individual subject performance. Blunted end of arrow represents baseline performance. Arrow heads correspond with 12-month visit performance.

m= meters; N = Newtons.

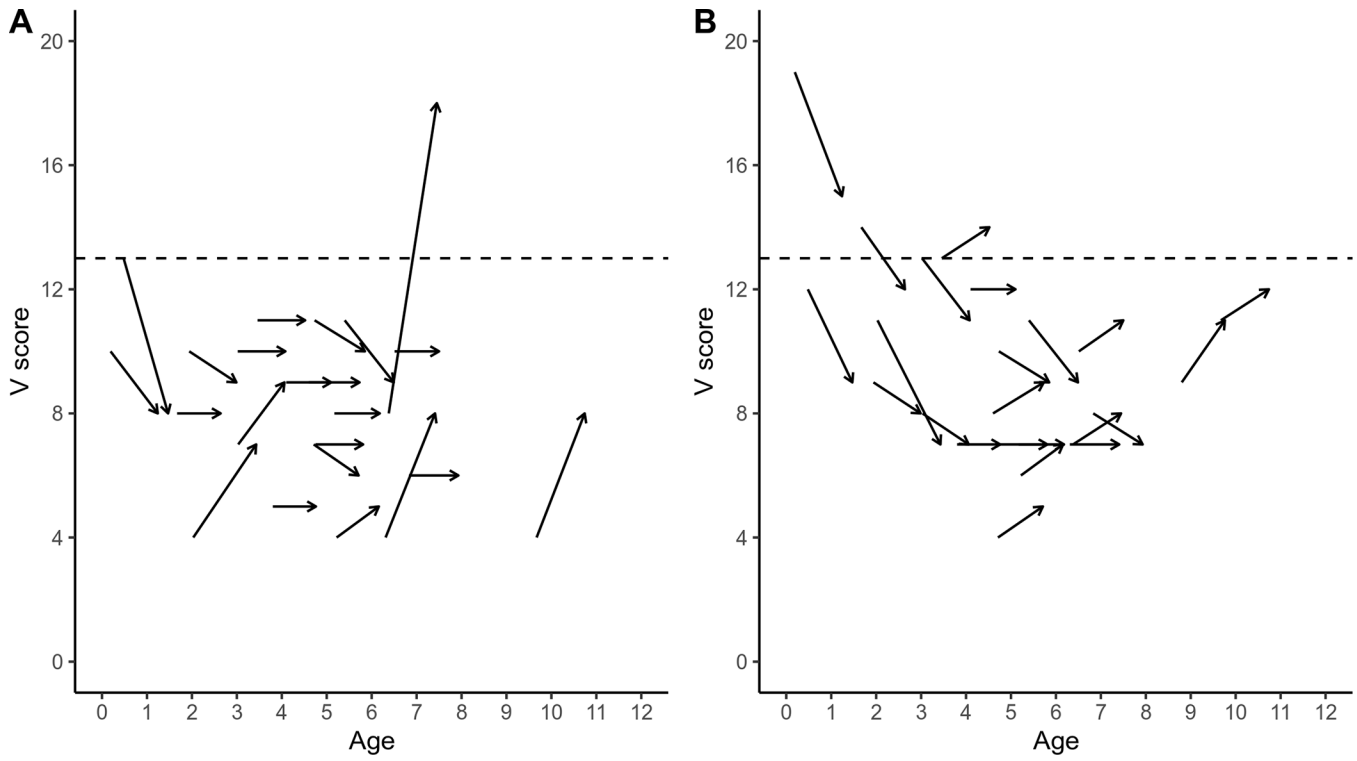

Figure 3: Vineland Adaptive Behavior Scale Gross and Fine Motor Subscales.

A) Gross Motor Subscale; B) Fine Motor Subscale. CDM participant performance from baseline to 12 month visits. Results above the dashed line (V-score = 13) are considered at least an “Adequate” level of adaptive functioning.

Table 1:

Baseline Characteristics.

Variable	CDM (n=47 unless otherwise indicated)
Age, years,	
Mean ±SD	6.41±3.64
Age group (n)	
<3 years of age	8
3–6 years of age	22
7–9 years of age	8
≥10 years of age	9
Gender, n (%)	
Male	25(53%)
Female	22(47%)
CTG_n repeats (n=40)	
0–499	4
500–999	10
1000–1499	16
1500–1999	8
2000+	2
Gestational Age, weeks (n=45)	
<35 *	12
35–37	10
8–41	22
>41	1
Respiratory Assistance, weeks (n=34)	
Mean ±SD	24.71±42.71
Range	0.3–156
ECG (n=38)	
Abnormal, clinically significant findings	
yes (n,%)	5 (13%)
no (n,%)	33 (87%)
Age at independent ambulation, months (n=30) †	
Mean ±SD	25.94±9.99
Range	11–60

* = Exact gestational age was available for 6 of the 12 participants born before 35 weeks. One participant was born at 29 weeks, the remainder were born between 30-37 weeks.

† = 2 children were below 12 months of age at time of evaluation and were excluded from calculation CDM = Congenital Myotonic Dystrophy, SD = Standard Deviation, ECG = Electrocardiogram

Table 2:

Mean percent change in performance from baseline to 12-month visit.

Variable	3–6 years	7–9 years	≥10 years
6 Minute Walk	n= 11 +35.92% **p=0.008**	n=7 +12.97% p=0.059	n= 8 −1.56% p=0.963
10 Meter Run *	n=11 −2.05% p=0.856	n=7 +0.30% p=0.962	n=7 +14.29% p=0.199
4 Stair Climb *, ascent	n=12 −55.33% p=0.138	n=8 −26.55% p=0.102	n=8 −6.66% p=0.343
4 Stair Climb *, descent	n=10 −28.31% p=0.111	n=8 −13.72% p=0.309	n=8 +5.92% p=0.565
Grip Strength	n=11 +3.75% p=0.777	n=6 +0.77% p=0.946	n=8 +23.12% p=0.091
Lip Force	n=9 +34.36% p=0.308	n=4 −1.06% p=0.978	n=7 +15.34% p=0.401

* = Negative values indicate faster completion, or better performance, of 10 Meter Run and 4 Stair Climb