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Delayed onset of ambulation in boys with Duchenne muscular dystrophy: Potential use as an endpoint in clinical trials

Jacob J. Gissy[a], **Teresa Johnson**[a], **Deborah J. Fox**[b], **Anil Kumar**[b], **Emma Ciafaloni**[c], **Anthonie J. van Essen**[d,†], **Holly L. Peay**[e,f], **Ann Martin**[f], **Ann Lucas**[f], **Richard S. Finkel**[a,g,*], and **the MD STARnet**

[a]University of Central Florida College of Medicine, Orlando, FL, USA [b]New York State Department of Health, Albany, NY, USA [c]University of Rochester, Rochester, NY 14627, USA [d]University of Groningen–University Medical Center Groningen, Netherlands [e]RTI International, Raleigh, NC, USA [f]Parent Project Muscular Dystrophy, Hackensack, NJ, USA [g]Nemours Children's Hospital, Orlando, FL, USA

Abstract

Individuals with Duchenne muscular dystrophy (DMD) often exhibit delayed motor and cognitive development, including delayed onset of ambulation. Data on age when loss of independent ambulation occurs are well established for DMD; however, age at onset of walking has not been well described. We hypothesize that an effective medication given in early infancy would advance the age when walking is achieved so that it is closer to age-matched norms, and that this discrete event could serve as the primary outcome measure in a clinical trial. This study examined three data sets, Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*); Dutch Natural History Survey (DNHS); and Parent Project Muscular Dystrophy (PPMD). The distribution of onset of ambulation in DMD (mean ± SD) and median age, in months, at the onset of ambulation was 17.3 (±5.5) and 16.0 in MD STAR*net*, 21.8 (±7.1) and 20.0 in DNHS, and 16.1 (±4.4) and 15 in PPMD. Age of ambulation in these data sets were all significantly later ($P < 0.001$) than the corresponding age for typically developing boys, 12.1 (±1.8). A hypothetical clinical trial study design and power analyses are presented based on these data.

Keywords

Duchenne; DMD; Walking; Ambulation; Motor development; Clinical trial

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disease that affects 1 in 3500 to 7000 males ages 5 to 9 in the U.S. [1]. Deletions, duplications or point mutations in the DMD gene cause absent, reduced or defective dystrophin in muscle [2]. Affected males

*Corresponding author. Nemours Children's Hospital, 13535 Nemours Parkway, Orlando, FL 32827, USA., rfinkel@nemours.org (R.S. Finkel).

†Deceased.

exhibit delayed motor development and eventual deterioration, and have a higher rate of cognitive challenges [3]. Boys with DMD present their first signs or symptoms at a mean age of 2.5 years, with mean age at diagnosis of five years when there are no prior affected family members [4]. Without intervention, loss of independent ambulation occurs in DMD by age 12 years, along with progressive cardiovascular, orthopedic, and respiratory complications [5]. Death occurs typically in the third or fourth decade, primarily as a result of respiratory or cardiac failure [6].

Walking independently is a fundamental motor milestone, innately driven as the motor system matures, and is clinically meaningful in neuromuscular disorders. This metric requires no medical evaluation, is something that children achieve spontaneously, and can be captured as a historical milestone. Normally developing children in the World Health Organization Multicentre Growth Reference Study Group (WHO MGRSG) started walking independently at a mean age of 12.1 ± standard deviation (SD) 1.8 months, with a range of 8.2 to 17.6 months [7]. No significant differences in this milestone exist between boys and girls [8].

Data on age at loss of independent ambulation are well established for DMD and use of glucocorticoid medication has been reported to be associated with prolonged ambulation by two to three years. However, the age when boys with DMD first walk independently has had more limited study. Dubowitz reported a series of 65 boys with DMD where 26 (40%) were delayed in walking, defined as after 18 months of age, and in sitting and/or standing; and 8 (12%) were delayed in walking alone or walked by 18 months but were delayed in sitting and standing [9]. Mirski and Crawford recently reported, in a sample of 179 patients, that 42% of boys with DMD walk after 15 months of age [10], which is later than the 90th percentile for normally developing infants. They also have shown that delays in walking and cognitive impairment are highly correlated in DMD ($P \leq 0.0001$).

We hypothesize that a drug started in early infancy in boys with DMD will accelerate the time to independent ambulation and narrow the gap from that observed in normally developing boys.

The aims of this study are to analyze and report both prospective and retrospective data on the ages of first independent ambulation among individuals with DMD from three different data sources and to assess the feasibility of using this metric as a trait that can be modified through medical intervention and could serve as an end-point in clinical trials with on infants and toddlers with DMD.

2. Methods

2.1. MD STARnet

The Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*) is a population-based surveillance system funded by the United States Centers for Disease Control and Prevention (CDC) to retrospectively identify and longitudinally follow all individuals diagnosed with childhood-onset Duchenne or Becker muscular dystrophy (DMD/BMD) born since January 1, 1982, who resided in one of the participating sites

(Arizona, Colorado, Georgia, Hawaii, Iowa, and western New York). Surveillance started in 2004 for Arizona, Colorado, Iowa, and western New York. In 2005, Georgia was added and in 2008, Hawaii. Each case is retrospectively identified and followed. For older cases that were identified at the start of surveillance, this meant searching for medical records that were up to 20 years old. Since the initiation of surveillance, all retrospectively identified and newly diagnosed cases were prospectively followed by annual medical record abstraction through December 31, 2011 (for cases ascertained before 2011), December 31, 2012 (for cases ascertained in 2012), or until death or migration out of an MD STAR*net* site. Multiple source case finding methods were used to identify potential cases. Key clinical and diagnostic data were used to assign a case status (definite, probable, possible, female, asymptomatic, or not DMD/BMD), which was then reviewed by a committee of neuromuscular clinicians from all sites to validate the final case status [11]. A detailed description of the MD STAR*net* surveillance methodology has been published previously [12]. Public health authority or Institutional Review Board approval was acquired and maintained at each study site for the project duration.

For this study, a three-tiered strategy was employed to select males most likely to have the DMD phenotype. First, males were included if their first signs of muscle weakness were reported before age 5 years; second, males were included if they ceased ambulating before age 13 without steroid use, or before age 16 with steroid use, and third, when mutation type was known, only males with out-of-frame mutations were included. Of the initial 1054, exclusions were made if the case was missing age of first ambulation (n = 214); was female (n = 8); did not have the DMD phenotype explained above (earliest signs and symptoms at/after age 5 years: n = 199; without steroid use, either ambulation loss or last clinic visit after 13 years, or with steroid use, either ambulation loss or last clinic visit after 16 years: n = 56); had an in-frame mutation (n = 66); or had a case status of possible (n = 48). The final analytic sample from this dataset included 463 DMD cases. There was not a statistically significant difference between the 463 males included and the 591 excluded cases on race/ethnicity ($P = 0.08$), but the difference was significant for study site ($P = 0.004$). While only 29% and 36% of cases were included from two sites compared to an average of 47% in the other four sites, we elected to include the data from all six sites.

Abstractors documented the age of first ambulation based on one of the following: (1) on the initial medical history and physical examination from the consulting neurologist (MD STAR*net*); (2) from a parent questionnaire completed prior to a medical appointment when developmental milestones are mentioned; or (3) from the referring pediatrician's notes that accompany the child to the specialist. All three sources relied on parent recall.

2.2. DNHS

The Dutch natural history study (DNHS) of 473 boys with DMD was performed in 1982–1983 and included Dutch children born and diagnosed with DMD between 1961 and 1982 [13]. Patients were identified via inquiry of the neurologists, pediatricians, and rehabilitation specialists, the Dutch Muscular Dystrophy Association, Dutch National Medical Registration, Central Bureau of Statistics, and DMD patients from the Department of Medical Genetics in Groningen.

Classification of DMD in patients was based on a scoring system detailed in the original publication. Scoring was based on various factors such as overall clinical picture, creatine kinase levels, electromyogram, muscle biopsy, electrocardiogram, and family history. As part of this survey predates identification of the DMD gene, only 57 patients out of the 473 underwent genetic confirmation. The patients were evaluated in each category and awarded a corresponding number of points. The total value was then consolidated and the title (i.e. case status) of possible, probable, or certain DMD was given. Of the 473 patients in the sample, 95 were missing data on age of ambulation and therefore were excluded. Of the remaining patients, data analysis was only performed on patients categorized as certain DMD. This resulted in a total of 281 patients for the analysis.

2.3. PPMD

DuchenneConnect is an online, self-report registry and educational resource for individuals with Duchenne and Becker muscular dystrophy (DBMD) and carrier females. It was established by Parent Project Muscular Dystrophy (PPMD) in 2007. The Registry can be accessed at www.duchenneconnect.org.

There are currently over 3000 registrants in DuchenneConnect. The Registry is targeted toward individuals in the United States; however, individuals from any country can participate. To date, more than 100 countries are represented in the Registry. Before participating, each registrant must consent to participation and anonymous data sharing using an online consent.

Registry data are entered by parents/guardians of affected individuals and by individuals with DBMD. Each participant's data are accessed through a unique ID and password, which maintains security and allows participants to update their data. Participant data are curated by PPMD's DuchenneConnect Coordinators (certified genetic counsellors). Updates to participant accounts are requested at least every 12 months.

The Registry data are collected using patient reported medical history and outcomes surveys. The "First Steps" survey was developed for this study and was launched in November, 2014 on the DuchenneConnect website, where data were collected over 15 weeks. Registrants were recruited through emails, the DuchenneConnect website and Facebook page, and in monthly newsletters. PPMD also promoted the surveys through social media, newsletters, and website.

The DuchenneConnect survey included questions about age at first ambulation, how well the respondent remembered the date, if the parents had any concerns with learning, and the age of ambulation of any siblings. Patient diagnosis of DMD was self-reported and participants varied in whether there was clinical verification of diagnosis. Cases were excluded if the patient was missing age of first ambulation; the patient was female; the patient had a case status other than Duchenne (i.e. Becker, uncertain, or carrier.) A total of 481 participants filled out the survey with 115 being excluded, resulting in 366 in the final analysis.

2.4. Statistical analysis

Descriptive statistics are expressed as median with interquartile range (IQR) and minimum–maximum (range), and as mean ± standard deviation (SD) with 95% confidence interval (CI) of the mean. Normality was assessed using Shapiro–Wilk test, and homogeneity of variance was examined using Levene's test. Between-group comparison of age of independent ambulation by data source (i.e., DNHS, MD STAR*net*, and PPMD) was made using the Kruskal–Wallis test, and follow-up pairwise comparisons were made using Mann–Whitney *U* tests with Bonferroni correction (*P*-values evaluated at 0.05/3 = 0.017). Comparison of age of independent ambulation between each data source and the mean age for walking alone from the WHO MGRS group (i.e., 12.1 months) was conducted with separate one-sample *t*-tests. All tests were two-sided, and statistical significance was defined at *P*-values < 0.05 for omnibus tests, and *P*-values < 0.017 for follow-up pairwise tests. Statistical analyses were conducted using SPSS 22.0 (IBM; Armonk, NY).

Power analyses were made assuming a two-sided, independent samples *t*-test, 1:1 allocation ratio, and $\alpha = 0.05$. Simulations were made to include a range of acceptable power levels (i.e., 80%–95%), and a range of plausible and clinically meaningful effect sizes (i.e., Cohen's $d = 0.5–2.5$). This range of effect sizes includes various approximations of mean difference (i.e., 2–5 months)/pooled SD (i.e., 2–5 months). Power calculations were made using PASS 12 (NCSS; Kaysville, UT).

3. Results

3.1. Age of independent ambulation

Distribution of age of independent ambulation for all three data sources departed significantly from normally developing children (all $P < 0.001$; Fig. 1), and homogeneity of variance among the three groups was not observed ($P < 0.001$). Age of independent ambulation differed significantly by data source ($P < 0.001$; Table 1; analysis not including WHO MGRS). Boys from the DNHS data source walked significantly later (median = 20.0 months) than did boys from the MD STAR*net* (median = 16.0 months; $P < 0.001$) and PPMD (median = 15.0 months; $P < 0.001$) data sources. Age of ambulation did not differ significantly between MD STAR*net* and PPMD data sources ($P = 0.017$). Additionally, mean age of independent ambulation from all three data sources differed significantly from the mean age of walking alone from WHO MGRSG (all $P < 0.001$).

3.2. Power analysis for clinical trials

The significantly later age of independent ambulation observed in the DNHS data source may be because researchers did not include genetic confirmation on all participants, and might therefore have included patients with different diagnoses. For this reason, we made the assumption that MD STAR*net* and PPMD are closer approximations of the actual age of independent ambulation in boys with DMD, and subsequently used these combined data (n = 829) to conduct power analyses for clinical trial feasibility (Fig. 2). The largest sample size required based on included parameters is 105 boys per group – this corresponds to detecting an effect size of 0.5 months at 95% power.

4. Discussion

To determine effectiveness of clinical interventions, defined outcome measures are required. These include discrete time points such as age when independent ambulation is lost, when scoliosis surgery is first performed, or when mechanical ventilation support is needed; or continuous variables such as motor function scales or the six-minute walk test distance. Age of first independent ambulation may be another outcome measure that could be employed reliably in young children.

There are several methodological limitations of this study. First, retrospective data are used with recollection bias likely having a significant impact of the results. Second, there may be an overlap of participants in the MD STAR*net* and PPMD databases. Due to having only de-identified data, it was not possible to identify individuals common to both data sets or calculate the extent to which this in fact occurred. Third, the capture rate likely varied significantly among the three registries. The degree to which this may have affected the results is not known but may be a significant source of selection bias, more so in the PPMD voluntary registry than in the MD STAR*net* or DNHS epidemiological registries.

There are two additional factors not considered in this analysis. First, it would be important to consider genotype–phenotype relationships, as specific DMD mutations might affect age at onset of ambulation. This analysis was not possible within these three datasets. Second, the impact of cognitive impairment was not considered here and may well be an important factor in when a boy with DMD begins to walk. Both of these topics should be included in a prospective study and would need to be considered in the power calculation for sample size and in a covariate analysis of the data.

Using retrospective data from three different sources, we have shown that the estimated age of onset of ambulation in boys with DMD is statistically different compared to normally developing boys, which confirms earlier observations. Spikes in age of ambulation were observed at 12, 18, 24, 30, and 36 months, likely representing a “rounding” bias by parents reporting age of ambulation in half-year intervals rather than months (data not presented).

Pane et al. reported that all boys with DMD achieved independent ambulation between the age of 10 and 36 months, with a mean of 16.7 months, which is similar to our findings from the MD STAR*net* and PPMD [14]. This report also identified that children with mutations downstream of exon 44, which are associated with involvement of dystrophin isoforms expressed at high levels in brain, also had lower Developmental Quotients (DQ), thus suggesting a different mechanism underlying neurodevelopmental delay in young boys with DMD. This finding suggests that the specific site of the deletion in the *DMD* gene may modulate the expression of the motor phenotype.

A comprehensive review of early developmental milestones in boys with DMD by Cyrulnik et al., which was based on parental recollection, identified 70% of boys with delayed ambulation and 42% with early language delay, compared to 2% and 4% respectively in non-affected sibling controls [15]. A correlation was noted between delayed ambulation and delayed early language or behavioral problems, suggesting that motor delay may indicate an underlying central nervous system issue. Mirski et al. reported delayed ambulation (walking

on or after age of 16 months of age) present in 42% of 107 boys with DMD. The delay was twice as likely if the participant also had a cognitive delay [10].

For future studies, in keeping with the WHO definition, we suggest that the operational definition of age of independent walking is defined as the age when the child can take five or more steps on three occasions without using any parental or gait support or devices [16]. Ideally parents should report this milestone with confirmation via video or, in the absence of recording, the physician can verify in clinic. Cognitive development also needs to be captured, such as on a Bayley scale.

Unlike older children who can be tested reliably on the six-minute walk test or NorthStar Ambulatory Assessment, two widely used metrics in current DMD studies, infants and young children will require a measure that is more innately part of normal motor development and not dependent on extent of effort, attention or behavioral context [17]. Infants who present with a delay in motor skills, such as independent ambulation, could be identified and diagnosed by age two years, which is a mean of three years earlier than currently experienced. A potentially favorable intervention could conceivably be started within the first two years of life as compared to current studies at ages 4 to 7 years (e.g. Catabasis CAT-1004 and vamorolone), by which time the child is already overtly symptomatic and has a more advanced burden of disease [18,19]. A pilot study using the high-dose weekend prednisolone regimen in boys under 30 months of age is in progress and uses the Bayley III to characterize both motor and cognitive development [20].

With current feasibility of newborn screening for DMD, pre-symptomatic infants could be identified and the timeline for initiation of therapy could potentially be pushed back to the first few months of life. Newborn screening for DMD is ethically appropriate once there is an effective treatment option for the parents to consider. Drugs shown to be beneficial in older boys with DMD could then be evaluated in pre-symptomatic infants. It is in this scenario that age when ambulation is achieved would be an appropriate outcome measure to identify response to drug in a clinical trial. There are also risks to the parents that need to be considered, for example, the psychological impact on the parents for having their infant with DMD participate in a clinical trial during the “good years” of the disease, when the impact is rather modest.

In conclusion, we have reported the age of ambulation in boys with DMD and discussed the feasibility of using this metric as a primary outcome measure in a clinical trial where an intervention would be initiated in early infancy. Additional prospective data are necessary to confirm these observations and also address if concomitant cognitive delays are associated with delayed ambulation. These data will permit construction of a more securely designed clinical trial for infants with DMD.

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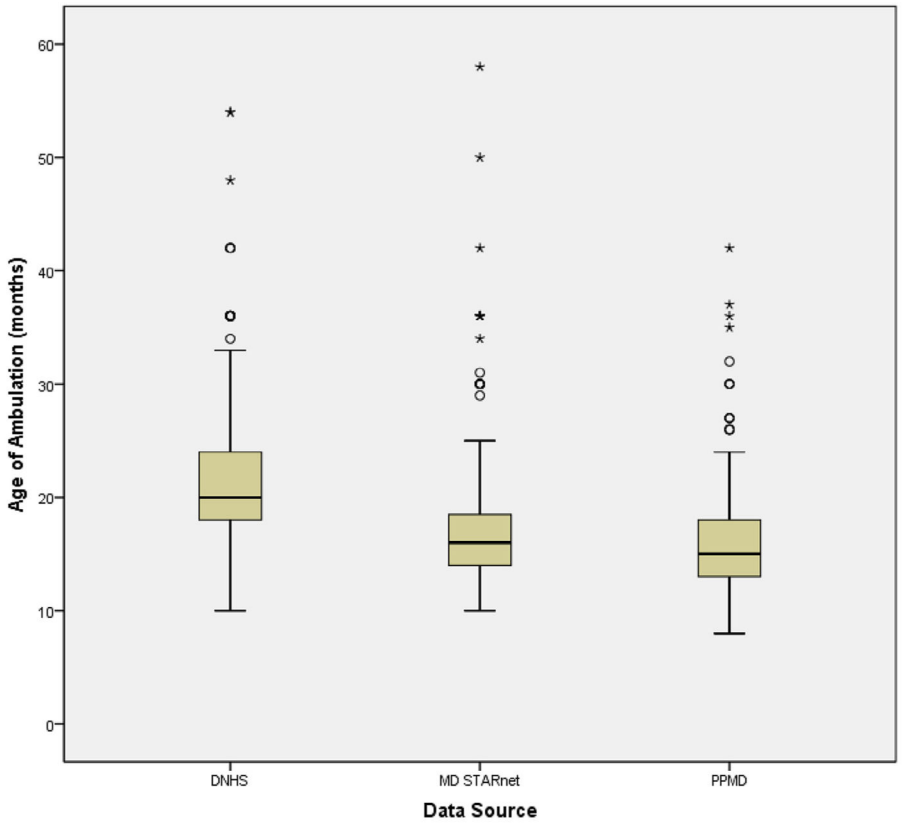

Fig. 1.

Boxplots[1] for age of ambulation by data source. [1]Line inside box represents the median or 50th percentile; lower and upper bounds of the box represent the 25th and 75th percentiles, respectively (shaded box is the interquartile range); lower T-bar represents the minimum value, and upper T-bar extends to 1.5 times the height of the box; circles indicate outliers (values outside the T-bars), and asterisks indicate extreme outliers (values extending >3 times the height of the box). DNHS = Dutch Natural History Study; MD STAR*net* = Muscular Dystrophy Surveillance, Tracking, and Research Network; PPMD = Parent Project Muscular Dystrophy.

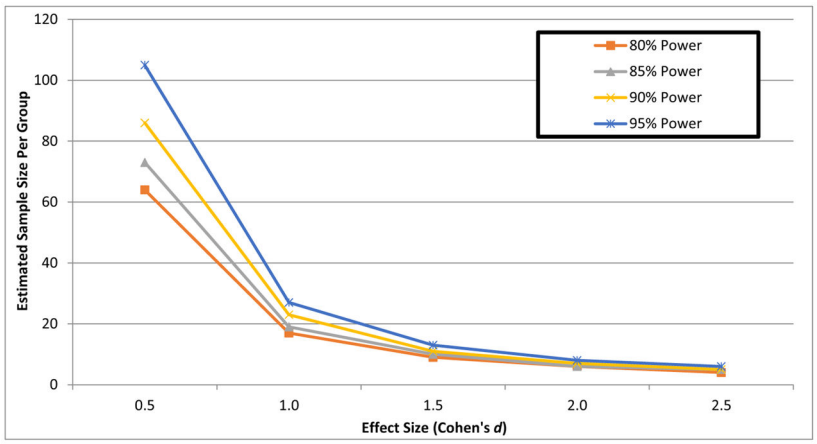

Fig. 2.
Estimated sample size by effect size and power level.

Table 1

Age of ambulation by data source and compared to WHO MGRS.

Data source	*N*	Age of ambulation (months)		Comparison to WHO MGRS	
		Median (IQR) (Range)	**Mean ± SD (95% CI)**	***P*-value**	**Mean difference (95% CI)**
DNHS	281	20.0 (18.0–24.0) (10–54)	21.8 ± 7.1 (21.0–22.7)	<0.001	9.7 (8.9–10.6)
MD STAR*net*	463	16.0 (14.0–18.5) (10–58)	17.3 ± 5.5 (16.8–17.8)	<0.001	5.2
PPMD	366	15.0 (13.0–18.0) (8–42)	16.1 ± 4.4 (15.7–16.6)	<0.001	4.0
WHO MGRS	816	12.0 (11.0–13.1) (not available)	12.1 ± 1.8 (not available)		

WHO, World Health Organization Multicentre Growth Reference Study Group; DNHS, Dutch Natural History Study; MD STAR*net*, Muscular Dystrophy Surveillance, Tracking, and Research Network; PPMD, Parent Project Muscular Dystrophy; IQR, interquartile range; Range, minimum–maximum; SD, standard deviation; CI, confidence interval.