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

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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 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

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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 STAR*net

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