Patterns of Growth in Ambulatory Males with Duchenne Muscular Dystrophy

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Objective To provide weight-for-age, height-for-age, and body mass index-for-age growth reference standards for ambulatory, steroid-naïve males, ages 2-12 years, with Duchenne muscular dystrophy (DMD) and to compare these growth curves to the 2000 Centers for Disease Control and Prevention growth charts for boys, which serve as references of physical size and growth for the general male pediatric population in the US.

Study design Through a multi-state population-based surveillance of individuals with muscular dystrophy, a total of 1877 weight and 1544 height measurements ascertained during 1985-2010 from 513 males with DMD were obtained retrospectively from medical record review. Cases were classified as DMD if loss of ambulation occurred before the 12th birthday or, if younger than 12 years and still ambulating, the earliest symptoms of dystrophinopathy occurred before the 6th birthday. Each growth chart was constructed using 5 percentiles: 10th, 25th, 50th, 75th, and 90th. Smoothing procedures were applied in 2 stages to the irregular plots of the empirical percentile values.

Results A set of growth curves, derived from a large cohort of male youth with DMD, are presented. These curves demonstrate that DMD males are shorter and tend to the extremes of weight and body mass index compared with the general male pediatric population in the US.

Conclusion Charts representing the pattern of growth in ambulatory, steroid-naïve males with DMD can facilitate monitoring of growth and early detection of unusual growth patterns. Use of these growth standards also will assist in monitoring responses to corticosteroid treatment. *(J Pediatr 2013;163:1759-63)*.

Muscle wasting and increased fat mass are hallmark characteristics of males with Duchenne muscular dystrophy (DMD).[1] In this recessive X-linked disorder, mutations in the dystrophin gene result in absent or reduced expression of the protein dystrophin, which leads to progressive muscle weakness, degeneration of muscle, and replacement of muscle with fat and fibrosis.

Patients with DMD can be at risk for both weight gain/obesity and weight loss/underweight at different times during the natural course of the disease.[2] Decreased energy expenditure from reduced mobility and diminished physical activity puts this population at increased risk of obesity.[3] Weight loss and undernutrition are often features of end-stage disease.[4,5] Short stature in affected males has been reported in studies based on small samples.[6-8] Differences in stature between affected and unaffected males appear to persist into adulthood, and short stature is present even when parental height is average.[6] It has been shown that males with DMD and non-affected males with similar body mass index (BMI) have a significant discrepancy in body composition.[7] Because body composition in males with DMD is characterized by decreased lean body mass and increased fat mass, comparison of BMI with growth references for the general pediatric population may not be informative of nutritional status.

Body composition changes, shifts between excessive weight gain and weight loss, and reduced height are characteristic features in males with DMD. Although standard growth charts such as the 2000 Centers for Disease Control and Prevention (CDC) growth curves[9] can be used to monitor longitudinal growth in DMD males, clinical appraisal of growth and nutrition status would be improved with unique growth charts.

Methods

A total of 513 males with DMD comprised the study population as part of the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). MD STARnet is a population-based surveillance system that aims to identify all individuals with Duchenne muscular dystrophy or Becker muscular

BMI	Body mass index
CDC	Centers for Disease Control and Prevention
DMD	Duchenne muscular dystrophy
DMD/BMD	Duchenne muscular dystrophy or Becker muscular dystrophy
MD STARnet	Muscular Dystrophy Surveillance, Tracking, and Research Network

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dystrophy (DMD/BMD) born since 1982 who have ever resided in 1 of the 5 participating sites (Arizona, Colorado, Georgia, Iowa, and western New York). Each participating site obtained permission for case finding and medical record abstraction either through institutional review board approval or by state-mandated public health reporting. The case-finding methodology used by MD STARnet is based on active review of source records in neuromuscular clinics, hospital discharge databases, private physician practices, service sites for children with special health care needs, and birth defect surveillance programs. Critical diagnostic elements of each abstracted record, including symptoms and age at onset, creatine kinase value, results of dystrophin mutation analysis testing, muscle biopsy reports, and family history, were reviewed independently by more than 4 clinicians and assigned to a case definition category of "definite" or "probable" by consensus.[10]

Criteria for "definite" DMD/BMD include symptoms related to a dystrophinopathy and either documented dystrophin mutation or muscle biopsy showing abnormality of dystrophin with no alternative explanation identified or elevated creatine kinase and pedigree compatible with X-linked inheritance and an affected family member. Criteria for "probable" DMD/BMD include symptoms related to a dystrophinopathy and elevated creatine kinase level and an X-linked pedigree consistent with a dystrophinopathy. Each study site maintains institutional review board approval for this research. Details of the surveillance methodology and case definition have been published previously.[11]

Classification of DMD was determined if loss of ambulation occurred before the 12th birthday or, if younger than 12 years and still ambulating, if the earliest symptoms of dystrophinopathy occurred before the 6th birthday. Valid signs or symptoms included a positive Gower's sign, abnormal gait, difficulty running or jumping, frequent falling, inability to keep up with peers, and gross motor delay or muscle weakness.

Other inclusion criteria for the present analysis included birth year from 1982 through 2008 and at least 1 recorded weight or height measurement within the age range of 2-12 years. Patients with other serious medical conditions that could affect growth were excluded: 4 patients with cerebral palsy, 1 patient with Crohn's disease, 1 patient with primary microcephaly, and 2 patients with spina bifida.

Weight and height data, demographic information, dates of initiation of corticosteroid and growth hormone treatment, and date of loss of ambulation were obtained retrospectively from annual medical record abstraction. Height and weight measurements recorded in medical records between November 1985 and July 2010 were extracted. Because of the likelihood that steroid use would induce weight gain and affect height velocity,[12] only weight and height measurements from growth periods prior to corticosteroid initiation (daily or intermittent regimes) were included to capture the natural history of growth in this population. Growth measurements obtained on those using a wheelchair full time were excluded because of the greater potential for measurement error.[13] In addition, measurements that were obtained after initiation of growth hormone therapy were excluded. After these exclusions, individual growth measurements were evaluated graphically and 46 height measurements and 19 weight measurements were removed for implausibility.

Statistical Analyses

Measurements at different ages were grouped into 6-month intervals and labeled as the midpoint of the interval, as follows: 2.00-2.49 years = 2.25 years, 2.50-2.99 years = 2.75 years… 11.50-11.99 years = 11.75 years. When multiple weight or height measurements had been made within any of the 6-month intervals for a single subject, the measurements were averaged and the averaged value was used for analysis.

Each growth chart was constructed using 5 percentiles: 10th, 25th, 50th, 75th, and 90th. To produce clinically useful percentile curves, smoothing procedures were applied in 2 stages to the irregular plots of the empirical percentile values, similar to the smoothing procedures used by the 2000 CDC Growth Charts for the US.[9] In the first stage, a locally weighted regression procedure was applied to each of the empirical weight-for-age, height-for-age, and BMI-for-age percentiles. This procedure applies a weight function to data in the neighborhood of the growth value to be estimated, so that measurements at ages that are close to the age-specific value to be estimated receive larger weights than those further away from the specified age. Each curve was further smoothed with a polynomial regression model fit to the midpoints of the age intervals to achieve the final curves.

Graphic comparison with the 2000 CDC growth charts was made to examine differences and similarities between the sets of reference curves. Further comparison between the Duchenne-specific growth curves and the CDC growth curves was accomplished by standardizing the Duchenne data using the CDC age-specific means and SD and then calculating a weighted average of the standardized scores across the age range.[9] The resulting standardized variables were compared using one-sample t tests.

Unlike the CDC data, which was collected from 5 cross-sectional surveys, our data included repeated growth measures for many of the DMD cases. To account for the within-subject correlation of our longitudinal data, we fit mixed-effects models to our data. The mixed-effects models provided an estimate of the central tendency of growth, in contrast to our empirically-derived percentiles of growth. To perform a sensitivity analysis, we first compared the DMD mean growth curves from the mixed-effects models with the corresponding CDC mean growth curves and tested for a statistical difference between each of the mean curves. Second, we compared the 50th percentile DMD curves, which were derived empirically, with the CDC 50th percentile curves. Finally, we evaluated the results from the comparison of the mean curves and the comparison of the 50th percentile curves for consistency.