

Categorizing natural history trajectories of ambulatory function measured by the 6-minute walk distance in patients with Duchenne muscular dystrophy

Eugenio Mercuri^{a,*}, James Edward Signorovitch^{b,c}, Elyse Swallow^b, Jinlin Song^b, Susan J. Ward^c for the DMD Italian Group[#] and the collaborative Trajectory Analysis Project (cTAP)⁺

^a Paediatric Neurology Unit, Catholic University, Rome, Italy

^b Analysis Group, Inc., 111 Huntington Ave, 10th Floor, Boston, MA, USA

^c The TAP Collaboration, One Broadway, 14th Floor, Cambridge, MA, USA

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Abstract

High variability in patients' changes in 6 minute walk distance (6MWD) over time has complicated clinical trials of treatment efficacy in Duchenne muscular dystrophy (DMD). We assessed whether boys with DMD could be grouped into classes that shared similar ambulatory function trajectories as measured by 6MWD. Ambulatory boys aged 5 years or older with genetically confirmed DMD who were enrolled in a natural history study at 11 care centers throughout Italy were included. For each boy, standardized assessments of 6MWD were available at annual intervals spanning 3 years. Trajectories of 6MWD vs. age and trajectories of 6MWD vs. time from enrollment were examined using latent class analysis. A total of 96 boys were included. At enrollment, the mean age was 8.3 years (mean 6MWD: 374 meters). After accounting for age, baseline 6MWD, and steroid use, four latent trajectory classes were identified as explaining 3-year 6MWD outcomes significantly better than a single average trajectory. Patient trajectories of 6MWD change from enrollment were categorized as having fast decline ($n = 25$), moderate decline ($n = 19$), stable function ($n = 37$), and improving function ($n = 15$) during the 3-year follow-up. After accounting for trajectory classes, the standard deviation of variation in 6MWD was reduced by approximately 40%. The natural history of ambulatory function in DMD may be composed of distinct trajectory classes. The extent to which trajectories are associated with novel and established prognostic factors warrants further study. Reducing unexplained variation in patient outcomes could help to further improve DMD clinical trial design and analysis.

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1. Introduction

Approximately one in every 3500 male births is affected by Duchenne muscular dystrophy (DMD), an X-linked disease arising from mutations to the dystrophin gene [1]. Early signs generally appear at 2–3 years of age, and include frequent falls and developmental delay [2]. Ambulatory function may

improve in younger patients due to age-related growth and development. However, disease progression eventually reverses these gains with progressive impairment of motor function and loss of ambulation by between 9 and 14 years on average, depending on the steroid regimen used [3,4] and subsequent progressive involvement of upper limb function [5,6].

Changes in ambulatory ability measured by the 6-minute walk distance (6MWD) test have been characterized in several longitudinal natural history studies [7–10], and this test has been used as the primary functional outcome measure for clinical trials of the first three disease modifying DMD treatments under investigation (ataluren, drisapersen and eteplirsen). At the time of reporting initial results from these trials, challenges were apparent in using 6MWD to measure treatment effects [11,12].

* Corresponding author. Paediatric Neurology Unit, Catholic University, Largo Gemelli 8, 00168 Rome, Italy. Tel.: +39 06 30155340; fax: +39 06 30154386.

E-mail address: eumercuri@gmail.com (E. Mercuri).

[#] Names are listed at the end of this article.

⁺ Names are listed at the end of this article.

In particular, rates of change in 6MWD showed significantly greater cross-patient variability than expected, resulting in limited statistical power to measure treatment effects with available sample sizes.

Variability in the rate of progression of 6MWD is known to be influenced by age, baseline 6MWD, and steroid use [2]. Longitudinal studies of 6MWD over 12, 24 and 36 months have identified a number of possible cut-off points that help to identify different profiles of progression, such as baseline 6MWD ≥ 350 meters and age ≥ 7 years [7,13,14]. On average, boys below the age of 7 have shown annual improvements on the 6MWD, while boys above the age of 7 have shown annual declines [7]. However, individual boys may show improving or declining function on either side of this age threshold.

In addition to variability in rates of progression from boy to boy, shorter-term, measurement-related variability has been characterized across repeated 6MWD assessments within individual boys. Although 6MWD is effort based, and can be influenced by motivation, test–retest reliability is high, with correlations exceeding 0.9. The variability in 6MWD that has frustrated clinical trials is primarily due to high inter-patient variability in rates of change rather than the smaller-scale, intra-patient measurement noise. For this reason, there remains a clear need for better characterizing the variability in 6MWD rates of change.

To objectively characterize the natural history of 6MWD in DMD, the present study sought to classify patients based on their trajectories of ambulatory function over time. Classification of patients based on disease trajectories has been used to understand natural histories in a number of diseases, including cardiovascular diseases and mental health conditions [15,16], and has been used to identify associations between patient outcomes and biomarkers [17] and to help interpret treatment effects in randomized trials [18–21]. We applied latent trajectory analysis to study the natural history of ambulatory function in DMD, as measured by 6MWD, and explored whether trajectory classes could help to further explain variation in disease progression after accounting for age, steroid use and baseline 6MWD.

2. Methods

2.1. Patient selection and outcomes measurement

The patients and outcomes included in this study have been previously described as part of an ongoing natural history study of DMD [9,10,22]. Included boys were enrolled at 11 tertiary neuromuscular care centers in Italy between January 2008 and June 2010. Inclusion required boys to have genetically confirmed DMD, to be aged 5 years or older, to be able to walk independently for at least 75 meters, and to be free of moderate or severe learning difficulties or behavioral problems. All boys fulfilling these criteria at the study centers were enrolled. The present study sample includes 96 boys with 3 years of annual 6MWD assessments conducted at the same study center at intervals of 12 ± 3 months. 6MWD was assessed at enrollment and annually according to the American Thoracic Society guidelines [23], with the modification of having two

examiners (one recording time and distances and one staying close to the patient for safety issues) [24]. The last follow-up visit in the study sample was performed in August 2013. Steroid use prior to and during follow-up was classified into three categories: no steroids, intermittent steroids, and daily steroids.

Only anonymous, de-identified data were analyzed in the present study. Data collection was approved by the Ethical Committees of all 11 of the participating centers. As the assessments were already part of the clinical routine in all centers, with the approval of the Ethics Committees, verbal consent to record the anonymized data in a database was obtained from the parents for the boys under age. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

2.2. Statistical analysis

The goal of this study was to characterize variation in 6MWD trajectories. A first step in characterizing variation is to measure its magnitude. The magnitude of variation in 6MWD outcomes has been widely reported in DMD, with standard deviations for annual change ranging from 80 to 100 meters. A next step, taken in this study, is to ask whether such a variable population might be better understood as a mixture of several distinct groups. Suppose, as a hypothetical example, that annual rates of change in 6MWD exhibited a bimodal distribution across patients with one peak around 50 meters of decline and another peak around 100 meters of decline. This distribution would suggest that the population can be treated as a composite of two groups, and that appropriately classifying patients (e.g., based on a cutoff somewhere between 50 and 100 meters of decline) would yield subgroups worthy of further characterization. In this hypothetical example the classification can be based on a single number (annual rate of decline).

Changes in ambulatory function in DMD, especially over the 3-year time period addressed in the current study, are complex and can include periods of both improvement and decline. They cannot be well characterized by a single number. For this reason, the present study employed a statistical method, latent class trajectory analysis, which extends the intuition applied in the hypothetical example above to settings in which each individual is characterized by multiple measurements over time. Considering all measurements, the method asks whether there are distinct peaks in the distribution across patients, i.e. clusters of patients that share similar trajectories.

Latent class trajectory analysis was also used to model annual 6MWD outcomes up to and including the first visit reflecting a loss of ambulation (defined as a 6MWD of zero meter). These analyses assessed whether the observed trajectories of 6MWD vs. age were adequately described by a single underlying mean trajectory or, alternatively, by a mixture of two or more underlying mean trajectories, with each mean trajectory corresponding to a latent class [25–27]. Within each latent class, mean 6MWD was modeled as a quadratic function of age, thus allowing for periods of increasing and decreasing 6MWD. Variation in 6MWD around the mean trajectory for each individual was modeled using a subject-specific random

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