Neuromuscular Disorders 18 (2008) 365–370

www.elsevier.com/locate/nmd

Corticosteroid treatment retards development of ventricular dysfunction in Duchenne muscular dystrophy ☆

Larry W. Markham [a,*], Kathi Kinnett [b], Brenda L. Wong [c], D. Woodrow Benson [b], Linda H. Cripe [b]

[a] *Monroe Carell, Jr Children's Hospital Vanderbilt University, Division of Pediatric Cardiology, 2200 Children's Way, Suite 5230, Nashville, TN 37232, USA*
[b] *Cincinnati Children's Hospital Medical Center, Department of Pediatrics Division of Pediatric Cardiology, Cincinnati, OH, USA*
[c] *Cincinnati Children's Hospital Medical Center, Department of Neurology, Cincinnati, OH, USA*

Received 22 January 2008; received in revised form 17 February 2008; accepted 4 March 2008

Abstract

Duchenne muscular dystrophy (DMD) is characterized by a predictable decline in cardiac function with age that contributes to early death. Although corticosteroids are a clinically effective pharmacologic therapy for skeletal muscle function, there is limited published work documenting the impact on cardiac function. The primary objective of this work is to determine benefit from steroid treatment on the development of ventricular dysfunction in DMD. We performed a historical cohort study of DMD cases undergoing serial cardiac evaluations from 1998–2006. In addition to the history of steroid use, basic medical characteristics and serial echocardiographic measures were obtained for each identified case meeting inclusion criteria. Data from initial (7.5 ± 0.8 years) and follow-up (12 ± 0.7 years) evaluation was collected from untreated ($n = 23$) and steroid treated ($n = 14$) DMD cases. Kaplan–Meier freedom from ventricular dysfunction was 93% for steroid treated cases versus 53% for untreated cases at 1500 days. Treatment with steroids was protective against ventricular dysfunction (Hazard ratio 0.16 95% CI 0.04, 0.70). We demonstrate here that steroid treatment, begun prior to ventricular dysfunction retards the anticipated development of ventricular dysfunction.

Keywords: Muscular dystrophy; Echocardiography; Prednisone; Deflazacort

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by a gene mutation that results in a greatly reduced or absent amount of the muscle protein dystrophin [1–3]. The phenotype is characterized by severe, progressive skeletal muscle weakness leading to loss of ambulation, respiratory failure, and death in the second to third decade of life [4,5]. Cardiac involvement associated with DMD leads to a rather predictable decline in cardiac function with age, resulting in ventricular dysfunction that contributes to early death from heart failure [5–9].

The long-term use of corticosteroids, initiated during childhood, in combination with aggressive pulmonary and cardiac care has improved the natural history of DMD, such that 53% of boys can now survive to 25 years of age [10]. Accordingly, chronic steroid therapy has become the standard of care for DMD [11]. Prolonged ambulation, reduced scoliosis and improved pulmonary function have been attributed to steroid use [11–13]. Despite these improvements, boys diagnosed with ventricular dysfunction continue to have a considerably shortened life expectancy compared to those without ventricular

Abbreviations: DMD, Duchenne muscular dystrophy; DBP, diastolic blood pressure; HR, heart rate; Ht, height; LVEDD, left ventricular end diastolic dimension; LVMi, left ventricular mass indexed; mWS, meridional wall stress; SBP, systolic blood pressure; SF, shortening fraction; VCFc, velocity of circumferential fiber shortening; VCFdiff, velocity of circumferential fiber shortening for the given wall stress; Wt, weight.

☆ No conflict of interest exists for the authors.

* Corresponding author. Tel.: +1 615 322 7490; fax: +1 615 322 2210.
E-mail address: Larry.Markham@vanderbilt.edu (L.W. Markham).

0960-8966/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.nmd.2008.03.002

dysfunction [10]. Further, there is limited published work documenting the impact of steroid treatment on the cardiac phenotype [14,15].

Thus, the primary objective of this work is to determine the benefit of steroid treatment on the development of ventricular dysfunction in DMD. For this purpose, we utilized a cohort of DMD boys undergoing cardiac evaluation before and after steroid treatment.

2. Materials and methods

2.1. Institutional oversight

With approval of the institutional review board, the clinical database was queried for all cases of Duchenne muscular dystrophy undergoing cardiac evaluation.

2.2. Inclusion criteria

The study is a historical cohort study of DMD cases undergoing serial cardiac evaluations from 1998–2006 based on the following criteria: (1) age less than 9 years old at initial evaluation, (2) steroid naive at initial cardiac evaluation, (3) minimum of 3 complete echocardiographic studies, each at least 1 year apart, (4) medical records for history of steroid exposure were complete and available. The diagnosis of DMD was based on the characteristic clinical phenotype and confirmation with lack dystrophin staining on muscle biopsy and/or dystrophin gene mutation.

2.3. Data acquisition

Demographic and clinical data were obtained for each identified case meeting inclusion criteria. The basic medical data included age, height, weight, and systolic and diastolic blood pressures at the time of echocardiogram. The medical record was reviewed for steroid exposure. All steroid treated cases had a cardiac evaluation performed prior to beginning treatment. Cases were assigned to the "treated" group if steroid treatment continued beyond 6 months. For all treated cases, the age at initiation and duration of treatment were noted.

2.4. Echocardiography

The serial echocardiographic measures included left ventricular dimensions, left ventricular mass, and the functional indices of shortening fraction (SF), and left ventricular meridional wall stress and contractility. All echocardiographic measurements were performed by a single observer (LWM) in the same manner prior to the medical record review to blind against steroid treatment.

Left ventricular dysfunction was defined by a shortening fraction of <28%. In DMD, the inherently poor echocardiographic windows seen with age result in inadequate visualization of the endocardial borders which decreases the accuracy of ejection fraction. When coupled with the simplicity and wide use of SF, we chose SF as the primary measure of ventricular function.

The wall stress contractility relationship is termed a load independent measure of systolic function because an increase in meridional wall stress corresponds to a decrease in contractility, which is independent of preload and accounts for afterload. Thus, a heart rate corrected velocity of circumferential fiber shortening (VCFc) below the lower confidence interval for a given wall stress is considered abnormal if the velocity of circumferential fiber shortening for the given meridional wall stress, or VCFcdiff, is a negative number [16]. By determining the expected contractility for a given wall stress based on these confidence intervals we can determine the VCFc difference for a given measure, indicating the deviation from expected. The stress velocity relationship was utilized as additional confirmation given the potential for steroid therapy to impact both preload and afterload.

2.5. Statistical analysis

Continuous variables were analyzed by Student's *t*-test, along with mixed repeat measure modeling for changes in respective variables with treatment over time. Frequencies were compared using Chi square and Fisher's exact test for the categorical variable outcome of ventricular dysfunction. Logistic regression, conditional on other covariables, was utilized to identify predictors of ventricular dysfunction. Regression models, such as Cox's Proportional Hazard model, were used to determine freedom from ventricular dysfunction.

3. Results

3.1. Study population

The Cardiology and Neurology clinical database search produced a total of 105 potential cases with the diagnosis of DMD. For this study, these potential cases were analyzed to ascertain information on inclusion criteria. The cases were then further analyzed to assure that complete echocardiographic data was available. Finally, the medical record was reviewed for steroid use. Of the 105 initial DMD cases identified, 37 individuals met the inclusion criteria.

3.2. Basic characteristics and echocardiographic measures

Untreated ($n = 23$) and steroid treated ($n = 14$) cases had a mean initial cardiac evaluation performed at 7.5 ± 0.8 years (untreated 7.6 ± 0.9 years, treated 7.5 ± 0.7 years). The final follow-up evaluation was performed at 12 ± 0.7 years. The basic medical data is outlined in Table 1. By Student's *t*-test comparison of initial and final basic medical data, the groups did not differ with respect to age, weight, heart rate, or blood pressure.