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CINRG Duchenne Natural History Study demonstrates insufficient diagnosis and treatment of cardiomyopathy in Duchenne muscular dystrophy

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Abstract

Introduction—Cardiomyopathy is a common cause of morbidity and death in patients with Duchenne muscular dystrophy (DMD).

Methods—A cross-sectional analysis of clinical data from a multi-institutional, international CINRG DMD Natural History Study of 340 DMD patients aged 2 to 28 years. Cardiomyopathy was defined as shortening fraction (SF) <28% or ejection fraction (EF) <55%.

Results—231 participants reported a prior clinical echocardiogram study, and 174 had data for SF or EF. The prevalence of cardiomyopathy was 27% (47/174), and it was significantly associated with age and clinical stage. The association of cardiomyopathy with age and clinical stage was not changed by glucocorticoid use as a covariate (P>0.68). In patients with cardiomyopathy, 57 % (27/47) reported not taking any cardiac medications. Cardiac medications were used in 12% (15/127) of patients without cardiomyopathy.

Discussion—Echocardiograms were underutilized, and cardiomyopathy was undertreated in this DMD natural history cohort.

Keywords

cardiomyopathy; Duchenne muscular dystrophy; glucocorticoid; echocardiogram; natural history

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive muscle disease characterized by progressive weakness resulting in premature death. It is the most common form of muscular dystrophy, affecting about 1 in 3800 – 6000 males.[1,2] The dystrophin gene defect causes absence of the muscle cytoskeletal protein dystrophin and leads to skeletal, respiratory, and cardiac muscle disease.[3] Cardiac disease is now the primary cause of mortality in over 20% of DMD patients, and proper diagnosis and treatment is an essential component of care in DMD.[4]

Diagnosis of cardiac dysfunction in DMD is often difficult, because patients are less active and do not develop classic early symptoms of heart failure such as exercise intolerance.[5] In order to diagnose cardiac disease appropriately, routine cardiac evaluation is necessary and recommended.[6] In 1990, Nigro *et al*. published data on cardiac disease in DMD patients studied between 1976 and 1987. Their findings demonstrated that preclinical disease was apparent in patients less than age 6 years, and cardiac disease increased over time until all

patients demonstrated pre-clinical or clinical disease over age 18 years.[7] They concluded that, as improvements in the treatment of skeletal and respiratory complications of DMD increase, a longer lifespan will permit increasing evidence of cardiac morbidity and mortality to emerge.

Through the Cooperative International Neuromuscular Research Group (CINRG), a clinical research network of academic centers, we collected natural history data from all participants in the CINRG Duchenne Natural History Study (DNHS) enrolled from 2006 to 2009.[8,9] These data provide the basis for a comprehensive description of cardiac disease in an international and representative population of individuals with DMD distributed throughout the DMD lifespan. The aims of this cross-sectional study were to characterize the patterns of cardiac investigation and to explore the correlation between cardiac function, age, clinical stage, and medication use from the first visit in the CINRG DNHS. An evolving understanding of cardiac disease in DMD may help formulate better diagnosis and treatment options and improve patient outcomes in the future.

Materials and Methods

Protocol approvals

The institutional review board or ethics review board at each participating institution approved the study protocol, consent, and assent documents. Informed consent/assent was obtained from each participant or his legal guardian prior to conducting study procedures.

Participants

A total of 340 participants were enrolled in the CINRG DNHS between May 2006 and July 2009. All participants were required to have: 1) clinical presentation and 2) genetic or muscle biopsy testing consistent with DMD. Data collected for these analyses were taken from prior echocardiogram results performed at CINRG sites and/or local cardiac referral centers and from reports of the participants at their baseline visit. Echocardiograms were not required for study inclusion and were not part of the study visit assessments.

Cardiac data

Participants completed a review of symptoms at the baseline visit that included cardiac symptoms and the names of current or past cardiac medications. Participants were designated “with cardiac medication” if they reported taking angiotensin converting enzyme inhibitors, beta-blockers, angiotensin II receptor antagonists, diuretics, and/or digoxin. Echocardiogram data were obtained from chart review and included the date of the last test prior to baseline visit and percentages for left ventricular ejection fraction (EF) and shortening fraction (SF). Echocardiogram images were not performed on a centralized protocol or centrally reviewed. Cardiomyopathy was defined as a reported EF<55% or SF<28% or both.[10–14]

Clinical stage classification

Functional grades using the Brooke and Vignos scales of upper and lower extremity, respectively, were collected at the baseline visit by centrally trained clinical evaluators. A

clinical stage classification was adapted from these 2 function scales and from consensus publications and participants were characterized by clinical stage into 4 groups reflecting progressive disability from early ambulatory to late non-ambulatory (Table 1).[15–19]

Glucocorticoids

Participants were categorized into 2 groups: “steroid naïve” or “with steroid”. “Steroid naïve” participants never received glucocorticoids (GC) or received GC for less than 1 month. Participants who were currently treated or treated for at least 1 month in the past with GCs were categorized as “with steroid”.

Statistical analysis

Several outcomes were evaluated in this analysis, including continuous measures of age, EF, and SF and categorical measures of presence of cardiomyopathy and clinical stage. For continuous outcomes, normality was tested and confirmed using the Shapiro-Wilk normality test. No normative transformations were necessary. Linear regression models were used to test the relationship between EF or SF and age and clinical stage. Logistic regression models were used to test the relationship between presence of cardiomyopathy and age and clinical stage. Each linear and logistic model was repeated with the addition of GC use (steroid naïve/with steroid) as a covariate. All tests were two-sided, and a P-value <0.05 was considered significant. The analysis of steroid use, where length of steroid duration was the dependent variable, utilized the student t-test on log-transformed data to compare mean duration between those with defined cardiomyopathy and those without. Stata version 11 (StataCorp, College Station, TX) was used for all analyses.

Results

Patient description

The CINRG DNHS enrolled 340 DMD patients across an age range from 2 to 28 years, average age of 12.0 years and median age of 11.1 years. Overall, 194/340 (57%) participants were ambulatory, 257/340 (76%) were “with steroid,” and 83/340 (24%) were “steroid naïve”. The distribution of ages, ambulatory ability, and GC treatment at study entry were reported previously.[8] Echocardiograms were available from chart review in 231/340 (68%) participants, and 174 (75%) reported results for SF, EF, or both.

Presence of cardiomyopathy

Based on echocardiography data from 174 participants, the diagnosis of cardiomyopathy increased from 5% of participants aged 0–5 years to 38% of participants aged 14–17 years and 61% of participants aged 18 years or older (Table 2). The mean age for development of cardiomyopathy in this cohort was 16.4±6.2 years at the time of the most recently recorded echocardiogram prior to enrollment. When analyzed as a continuous measurement, age was a significant predictor of the presence of cardiomyopathy (Table 3). In all cases, the impact of GC use as a covariate was not significant for the presence or absence of cardiomyopathy, nor was restriction of the analysis to participants not currently taking cardiac medications (Table 3 and data not shown). A total of 35 (20%) of the 174 participants who had echocardiogram data did not use GC (Table 2). Of the remaining 139 participants who were

GC users, 95% of participants with cardiomyopathy and 92% of participants without cardiomyopathy had received GC treatment for greater than 3 months.

Participants' self-assessments of cardiac symptoms were low. For participants with cardiomyopathy who responded to the questions (n=44), 11 (25%) reported feeling racing heart beats, 8 (18%) reported ankle or leg swelling, 6 (14%) reported symptoms of "congestive heart failure," and 5 (11%) reported chest pains. The mean EF for participants reporting symptoms of "congestive heart failure" was 38±11% (n=5). It is unknown if these symptoms were directly related to cardiac causes. Of the 47 participants who met criteria for cardiomyopathy, only 20 (43%) were treated with cardiac medications.

Of these, 11 were treated with angiotensin converting enzyme inhibitors (ACEi), 4 were treated with ACEi and beta-blockers (BB), 3 were treated with ACEi, BB, and digoxin, and 2 were treated with ACEi and digoxin. Of the 127 participants without cardiomyopathy, 15 (12%) were treated with cardiac medications, including 11 with ACEi, 2 with ACEi and digoxin, 1 with BB, and 1 with BB and digoxin.

Clinical Stage

A total of 162 participants had data from echocardiograms and a clinical stage determination and were included in this analysis (Table 4). Of the participants analyzed, 134 (83%) were treated with GCs either currently or in the past. Thirty-five (22%) participants were treated with cardiac medications.

Table 4 shows the analysis of the dichotomous cardiomyopathy diagnosis with clinical stage by logistic regression. There was significantly increased prevalence of cardiomyopathy in the late non-ambulatory stage and a trend towards increased presence of cardiomyopathy in the early non-ambulatory stage. EF and SF were associated significantly with clinical stage such that a more severe clinical stage corresponded to a decrease in EF and SF (Supplementary Table 1). Specifically, participants in the late non-ambulatory stage had an EF that was decreased significantly over those in the early ambulatory stage. While only the participants in the late non-ambulatory stage had significantly lower EF values, there was a significant overall trend in the association ($P = 0.007$). The addition of GC use as a covariate did not have a significant effect on the association between clinical stage and cardiomyopathy, SF, or EF. Limiting the analysis to those not currently taking cardiac medications did not change the interpretation of the association of cardiomyopathy with clinical stage (data not shown).

Discussion

Results from the baseline data of cardiac disease in DMD from a multi-center, multi-national natural history study demonstrate a significant disease burden from cardiomyopathy based on echocardiogram findings alone. The mean age for development of cardiomyopathy of age 16.4 years was determined based on the age of the last recorded echocardiogram prior to enrollment. Previous studies showed a range of ages from 13.2 to 14.1 years, which was based on the age of first abnormal echocardiogram.[20,14] Nearly 15% of participants between ages 6 and 13 years met criteria for cardiomyopathy, and this increased to over 50% of

participants older than age 14 years. Age was a significant predictor of cardiomyopathy and negatively correlated with EF and SF measures. Surprisingly, 32% of subjects enrolled in the CINRG DNHS did not report having a clinical echocardiogram by the time of their first visit in the CINRG DNHS. Of these, approximately one-third were 10 years or older, a cohort that demonstrated a 34% prevalence of cardiomyopathy in those who did have an echocardiogram at baseline. Also concerning is that greater than half of the participants with cardiomyopathy reported no treatment with cardiac medications at baseline. Previous studies support the therapeutic benefit of pharmacological treatment of cardiomyopathy in DMD patients.[10,21–23,20,24] Our findings suggest that under-treatment of cardiomyopathy in DMD could be a significant cause of comorbidity.

There is wide variability in past reports of the prevalence of cardiomyopathy using echocardiography in DMD patients. The largest study correlating age with incidence and age of onset of cardiomyopathy was Nigro *et al*. (1990).[7] The age groupings in our study were consistent with that study, however the previous study used a definition of cardiomyopathy based on an EF<45% and broader electrocardiogram (ECG) and echocardiogram criteria in a cohort of 328 Italian DMD patients. Nigro *et al*. also did not specify if their participants were treated with GCs and/or cardiac medications. Therefore, our study reports a lower incidence of cardiomyopathy for each age range studied, including a 61% incidence in participants older than 18 years. While it is often stated that all subjects with DMD greater than 18 years of age have evidence of cardiomyopathy, this refers to the more inclusive definition used in the Nigro *et al*. study including ECG changes and not solely echocardiogram measures of systolic function.

In the CINRG DNHS, age was a significant predictor for the presence of cardiomyopathy. Kirchmann *et al.* (2005) and Markham *et al*. (2008) also found that patient age had a significant impact on SF.[25,12] Several prior studies reported no correlation between cardiac involvement and patient age; however, most were limited by smaller sample sizes.[26–31] In our study, GC treatment was not shown to significantly affect the correlation between cardiomyopathy and age. In contrast, Markham *et al* (2008) suggested a protective effect of GC treatment on development of cardiomyopathy.[12]

Our study showed that cardiomyopathy is associated significantly with clinical stage when later stages were compared with the earlier least symptomatic stage, classified as early ambulatory. In particular, the strongest association was observed by comparing the late non-ambulatory stage with the early ambulatory stage. Few studies report both specific clinical stage and cardiac data. Van Brockel *et al*. (2009) found a 50% (7/14) prevalence of cardiomyopathy using ventriculography in late, non-ambulatory males on respiratory support, and Silversides *et al*. (2003) showed a 58% (7/12) prevalence of cardiomyopathy in non-ambulatory, GC naïve patients.[31,32] An association between decreasing EF and SF and increasing severity of clinical stage is inter-related with and confirms the association between cardiomyopathy, age, and clinical stage.

This study showed that GC treatment did not significantly impact the presence or absence of cardiomyopathy as assessed by prior echocardiogram result reported at study enrollment. The majority of participants received GC therapy for greater than a year. These results were

similar to prior reports by Gulati *et al*. (2005) and Kirchmann *et al.* (2005) that also demonstrated no significant correlation between cardiac involvement and GC therapy.[28,25] However, 2 recent studies demonstrate beneficial effects of GC therapy on cardiomyopathy. Barber *et al*. (2013) showed delayed onset of cardiomyopathy related to GC therapy.[33] Schram *et al*. (2013) showed that GC therapy, in addition to renin-angiotensin-aldosterone system antagonists, significantly improved survival over a 15 year follow-up period.[34] Other series reported stabilization of cardiac function with exposure to GCs (prednisone and/or Deflazacort).[35,11,13,31,12] Our analysis is limited by a relatively small number of GC naïve participants (n=35). Longitudinal follow-up of this cohort may provide additional insights into any impact of GC therapy on cardiomyopathy.

Interestingly, we found that 12% of participants without evidence of cardiomyopathy were taking cardiac medications. This included 5 of 52 who were less than age 10 years and 10 of 75 who were greater than age 10 years. One previous study, and the 10 year follow up, demonstrated a beneficial effect of angiotensin converting enzyme inhibitor therapy on cardiac function after 5 years and on mortality after 10 years.[10,21] Some practitioners prescribe cardiac medications prior to the onset of cardiomyopathy; however determination of the benefits of this practice requires further study.[36]

There are some potential limitations to this study inherent in a natural history cohort. However, these limitations are balanced by the inherent strength that the cohort reflects current clinical management. We were unable to obtain a complete dataset on the presence or absence of cardiomyopathy for all participants, because not all participants had echocardiography results for a variety of reasons including: 1) young age at enrollment, 2) as a function of the clinical care received, or 3) because EF and SF could not be measured on the clinical echocardiogram prior to enrollment. Furthermore, a limitation of using both SF and EF if available is that there may not be an exact correlation between the 2 measures. Also, this study did not collect data on preclinical markers of cardiomyopathy, including myocardial strain imaging or cardiac magnetic resonance imaging. However, these preclinical markers are not yet used broadly in the evaluation and management of DMD patients. Lastly, the limitations of a cross-sectional approach in the baseline dataset will be addressed in future studies by assessing longitudinal results in the CINRG DNHS.

In conclusion, this analysis of baseline data of the CINRG DNHS confirms the significant impact of cardiomyopathy in DMD. While few subjects with DMD may display overt clinical symptoms of cardiomyopathy, nearly 15% of participants who were age 6–13 years had decreased systolic function on echocardiogram. Cardiomyopathy was correlated significantly with age and clinical stage. Cardiomyopathy was underdiagnosed and undertreated in DMD patients included in this international cohort, which supports the need for increased physician awareness and further development of early cardiac treatment protocols for DMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACEi	angiotensin converting enzyme inhibitor
BB	beta blocker
CI	confidence interval
CINRG	Cooperative International Neuromuscular Research Group
DMD	Duchenne muscular dystrophy
DNHS	Duchenne Natural History Study
ECG	electrocardiogram
EF	ejection fraction
GC	glucocorticoids
OR	odds ratio
SF	shortening fraction

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Appendix

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Table 1

Definition of clinical stage evaluation used in the CINRG Duchenne Natural History Study based on functional grade.

Stage	Status	Functional grade		Definition
		Leg	Arm	
1	Early ambulatory	1	1	Normal or slight developmental delay
2	Middle/Late ambulatory	2–6	1–2	Progression to inability to climb stairs
3	Early non-ambulatory	7	1–3	Unable to walk, able to use upper limb
4	Late non-ambulatory	7	4–6	Unable to walk, limited use of upper limb

Table 2

Characteristics of CINRG Duchenne Natural History Study participants who had echocardiogram data.

	Age group (% exhibiting cardiomyopathy)					Total
	2–5y (5%)	6y–9y (18%)	10y–13y (12%)	14y–17y (38%)	≥18y (61%)	
Cardiomyopathy	**1**	**7**	**6**	**11**	**22**	**47**
Cardiac medications	0	2	2	5	11	20
Current or past steroid user	0	2	2	4	9	17
Steroid naive	0	0	0	1	2	3
No cardiac medication use	1	5	4	6	11	27
Current or past steroid user	1	5	4	6	5	21
Steroid naive	0	0	0	0	6	6
No cardiomyopathy	**19**	**33**	**43**	**18**	**14**	**127**
Cardiac medications	2	3	3	4	3	15
Current or past steroid user	0	3	3	2	3	11
Steroid naive	2	0	0	2	0	4
No cardiac medication use	17	30	40	14	11	112
Current or past steroid user	6	26	39	11	8	90
Steroid naive	11	4	1	3	3	22
Total	**20**	**40**	**49**	**29**	**36**	**174**

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Table 3

The relationship between a diagnosis of cardiomyopathy and age.

Outcome	Model	Covariates	N	OR/coefficient	95% CI	p-value	r^2	Steroid OR/coefficient (p-value)
Diagnosis of cardiomyopathy	Logistic	none	174	1.20	1.12 – 1.29	<0.001	N/A	N/A
		Steroid	174	1.20	1.12 – 1.29	<0.001	N/A	1.14 (0.788)
EF	Linear	none	127	−0.92	−1.22 – −0.60	<0.001	0.212	N/A
		Steroid	127	−0.92	−1.22 – −0.60	<0.001	0.215	−1.57 (0.502)
SF	Linear	None	143	−0.38	−0.56 – −0.20	<0.001	0.109	N/A
		Steroid	143	−0.38	−0.57 – −0.20	<0.001	0.109	0.036 (0.975)

EF – ejection fraction; SF – shortening fraction; OR – odds ratio measuring the likelihood of a cardiomyopathy diagnosis with increasing age,; CI – confidence interval; r^2 – correlation coefficient for the model describing how much of the variation in outcome can be explained by the terms in the model

Table 4

The relationship between cardiomyopathy and clinical stage.

Co-variate	Clinical stage	Defined CM		Age mean (range)	OR	95% CI	P-value	Steroid OR (p-value)
		No	Yes					
None	Early ambulatory	34	4	8.2 (5.0 – 13.7)	1.00			N/A
	Middle/Late ambulatory	32	11	10.8 (5.1 – 16.7)	2.92	0.84 – 10.12	0.091	
	Early non-ambulatory	16	7	14.1 (10.2 – 18.8)	3.72	0.95 – 14.56	0.059	
	Late non-ambulatory	34	24	18.7 (9.4 – 28.0)	6.00	1.88 – 19.14	0.002	
Steroid	Early ambulatory	34	4	8.2 (5.0 – 13.7)	1.00			1.22 (0.679)
	Middle/Late ambulatory	32	11	10.8 (5.1 – 16.7)	2.93	0.85 – 10.14	0.090	
	Early non-ambulatory	16	7	14.1 (10.2 – 18.8)	3.69	0.94 – 14.45	0.061	
	Late non-ambulatory	34	24	18.7 (9.4 – 28.0)	6.16	1.92 – 19.81	0.002	

OR – odds ratio measuring the likelihood of a cardiomyopathy diagnosis with each increasingly severe clinical stage; CI – confidence interval; CM – cardiomyopathy