Characteristics of Duchenne and Becker Muscular Dystrophy Patients in the Pediatric Cardiomyopathy Registry

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ABSTRACT

Background: The NHLBI-sponsored PCMR is a multicenter study of pediatric cardiomyopathy (CM) in North America. Data have been collected on patients with Duchenne (DMD) and Becker (BMD) muscular dystrophy. **Methods:** As of May 2003, the Registry is comprised of 2,602 children and adolescents who presented to a pediatric cardiologist with CM from 1990 to present. Inclusion criteria include 1) ≤18.0 years of age at time of CM diagnosis; 2) echocardiographic evidence of CM, defined as ≥2 left ventricular measurements (ejection fraction, posterior wall thickness, septal thickness, end diastolic dimension or volume) exceeding 2 standard deviations or an echocardiographic pattern of CM; 3) a pathologic diagnosis of CM on autopsy; or 4) other clinical evidence provided by the cardiologist. **Results:** The PCMR includes 134 patients with DMD or BMD. 99% are male, and 27% are non-white. We observed 39 DMD and 1 BMD deaths; 0 DMD transplants and 6 BMD transplants, for a total of 39 DMD and 7 BMD death/transplant events. 25% of all DMD patients die within 2.2 years following CM diagnosis (defined as meeting PCMR entry criteria) and 50% die within 5.3 years (p=.219 vs. BMD). 25% of all BMD patients die or are transplanted within 0.4 years following CM diagnosis and 50% die or are transplanted within 1.3 years (p=.063 vs. DMD). At diagnosis patients with BMD are somewhat more likely (p=.143) to have mitral regurgitation (60% vs. 24%), particularly those with congestive heart failure (100% vs. 40%), and a higher LV end diastolic dimension(3.0 vs. 1.3 BSA-adjusted Z-score, p=.002) than patients with DMD. Similarities between the two groups include a mean age of CM diagnosis of 14 years, with one-third having congestive heart failure at enrollment. Non-muscular dystrophy patients in the PCMR have a lower mortality rate than the BMD/DMD group (p≤0.0001). **Conclusions:** Current observations suggest that the DMD/BMD groups have different clinical characteristics at the time of CM diagnosis, with mitral regurgitation, LV dilation and heart failure being more common in the BMD patients. Following diagnosis for CM, DMD patients have a higher mortality rate and BMD patients may have a higher transplant rate than pediatric patients with other types of CM.

OBJECTIVE

To determine the characteristics of patients with Duchenne (DMD) and Becker (BMD) muscular dystrophies from the time of meeting criteria for cardiomyopathy and their subsequent clinical course.

BACKGROUND

The dystrophinopathies, including Duchenne muscular dystrophy (DMD), Becker muscular Dystrophy (BMD) and X-linked dilated cardiomyopathy (XLDCM) are X-linked inherited disorders of muscle that lead to myocyte necrosis and generalized muscle weakness. Molecular studies have led to the identification of defects in the Dystrophin gene, or regulatory genes associated with the Dystrophin gene as the cause of these forms of muscular dystrophy[i],[ii]. Onset of skeletal muscle weakness and respiratory symptoms start at a young age, as do electrocardiographic abnormalities.[iii]. The electrocardiographic abnormalities correlate with pathologic changes in the myocardium. Although cardiomyopathy is present on a cellular/histological level, onset of echocardiographic abnormalities, clinical cardiomyopathy and cardiovascular symptoms are usually delayed until the second decade of life in DMD[iv] and XLDCM[v] and the third decade of life in BMD[vi]. Until recently, death in DMD often occurred around 15 to 20 years of life due to respiratory complications or cardiac dysfunction (congestive heart failure and or arrhythmias). With intensive respiratory care, however, many affected individuals with DMD now live into their late 20s and older[vii]. This will make cardiac function and cardiovascular health an increasingly important part of the disease process in DMD.

The NHLBI-sponsoredPediatric Cardiomyopathy Registry (PCMR) is a multicenter study of pediatric cardiomyopathy in North America. Data have been collected on patients with Duchenne (DMD) and Becker (BMD) muscular dystrophy. As of December 2003 the PCMR includes extensive longitudinal data on 134 children with a diagnosis of DMD or BMD who were diagnosed with cardiomyopathy between 1990 and 2003. This is a fairly homogenous group of subjects, although there are differences due to local practice patterns in terms of therapy. Some cardiologists now use anti-congestive therapies such as ACE inhibitors and/or β-blockers in the treatment of adult dystrophinopathy patients with heart failure. There is evidence that these therapies have a short-term beneficial effect in this population, causing a decrease in heart failure symptoms, improved left ventricular ejection fraction, and an improved neurohormonal state (Ishikawa, Bach, Ishikawa, et al.[viii], 1995; Ishikawa, Bach, Minami, 1999[ix]). Invasive and non-invasive ventilation has also been used for treatment of ventilatory insufficiency in patients with dystrophinopathies, and may have beneficial cardiovascular effects (Melacini, Vianello, Villanova, et al., 1996[x]). There is no information available to determine how widespread the use of these therapies is or what their long-term effects are in children with DMD and BMD.

The PCMR database currently includes data on DMD and BMD patients only from the time that patients meet PCMR inclusion criteria for dilated cardiomyopathy. Data are available for many patients prior to this, but are not entered into the database. We reviewed the database to determine the characteristics of patients at the time of meeting PCMR criteria for entry into the database to determine the characteristics of these patients at diagnosis and predictors of outcome.

METHODS

Pediatric Cardiomyopathy Registry Eligibility Criteria

The PCMR was funded by the NHLBI in 1994. As of December 2003, the Registry was comprised of 2,882 children and adolescents who presented with cardiomyopathy to a pediatric cardiologist from 1990 to present. Inclusion criteria include 1) less than 18.0 years of age at the time of cardiomyopathy diagnosis; 2) echocardiographic evidence of cardiomyopathy, defined as at least 2 left ventricular measurements (ejection fraction, posterior wall thickness, or end diastolic dimension or volume) exceeding 2 standard deviations for age (ejection fraction) or for body surface area (posterior wall thickness, end diastolic dimension or volume); or 3) an echocardiographic pattern of cardiomyopathy including localized ventricular hypertrophy or restrictive cardiomyopathy or a contracted form of endocardial fibroelastosis; 3) a pathologic diagnosis of cardiomyopathy on endomyocardial biopsy or autopsy; or 4) other clinical evidence provided by the cardiologist (Grenier, Osganian et al., 2000[xi]). 15 clinical exclusion criteria were used. These are: 1) Endocrine disease known to cause heart muscle disease; 2) History of rheumatic fever; 3) Toxic exposures known to cause heart muscle disease; 4) HIV infection or born to an HIV positive mother; 5) Kawasaki disease; 6) Congenital heart defects unassociated with malformation syndromes; 7) Immunologic disease; 8) Invasive cardiothoracic procedures or major surgery during the preceding month, except those specifically related to cardiomyopathy including LVAD, ECMO, and AICD placement.; 9) Uremia, active or chronic; 10) Abnormal ventricular size or function that can be attributed to intense physical training or chronic anemia; 11) Chronic arrhythmia, unless there are studies documenting inclusion criteria prior to the onset of arrhythmia; 12) Malignancy; 13) Pulmonary parenchymal or vascular disease; 14) Ischemic coronary vascular disease; 15) Association with drugs known to cause hypertrophy. Due to limited resources, patients with only a family history of cardiomyopathy and/or subclinical evidence only of cardiomyopathy are not included in the database.

Data Collection

Data were collected by site visitors who reviewed data from patient charts and clinical databases at participating centers. Data was entered into the ADEPT database maintained by New England Research Institutes (NERI). Quantitative echocardiographic data was obtained from reports and entered into the database where measurements were assigned body surface area-adjusted Z-scores.

Statistical Analysis

Results are reported as p-values with a significance level of $p < 0.05$. The DMD and BMD groups were compared to each other as well as to patients with other neuromuscular diseases (N=85) and to patients with non-neuromuscular and idiopathic disease (N=2568). Statistical analysis was performed at NERI.

RESULTS

There were 2792 patients enrolled in the PCMR through December 2003 who were included in this analysis. 23 centers reported 140 patients with DMD or BMD. Of these 124 were identified as having DMD and 15 as having BMD by the enrolling institutions. The one female patient in the BMD group was eliminated after review revealed that she most likely had a muscular dystrophy not related to Dystrophin deficiency (most likely Emery-Dreifus muscular dystrophy). The remaining 139 patients were analyzed for characteristics at the time of diagnosis and for survival (Table 1).

Time to Death or Transplant following diagnosis of CM

We observed 44 DMD and 0 BMD deaths; 0 DMD transplants and 6 BMD transplants. In the Other neuromuscular (Other NM) disease group, there were 7 deaths and 4 transplants. Due to the small size of the BMD group the median survival time and related CI's were not estimable. In the non-muscular dystrophy (Non-MD) cohort the death rate never reached 50%. Figures 1 displays survival and Figure 2 displays event-free survival (i.e., time to death or transplant combined).

Table 2 shows that 25% of all DMD patients die within 2.2 years following diagnosis of clinical CM and 50% die within 5.4 years of diagnosis of CM (p=.219 vs. BMD). DMD survival is marginally different from BMD patients (logrank p=.065, Gehan-Wilcoxon p=.091 which weights earlier differences more heavily).

Table 3 shows that 25% of all BMD patients die or are transplanted within 0.4 years following diagnosis of clinical CM, and half of all DMD+BMD cases die or are transplanted within 5.7 years, a much shorter time than for Non-NM disease (half die or are transplanted within 11.5 years). There was no significant difference in DMD vs. BMD event-free survival (logrank p=.218), but weighting earlier differences more heavily there was (Gehan-Wilcoxon p=.026).

Echocardiographic Data

Table 4. shows there is a higher grade of mitral regurgitation in BMD than in DMD patients (linear trend p=.048), and that the BMD patients have a larger left ventricular end-diastolic and end-systolic diameter Z-score (p=.003 and .024).

Table 1. Demographics, Medical History and Clinical Characteristics by Etiology All patients have met PCMR enrollment criteria (i.e., clinical expression of cardiomyopathy).

Characteristic	DMD	BMD	DMD vs. BMD p-value	DMD+BMD	Other NM Disease	Non-NM & Idiopathic Disease	3-group p-value
N	124	15		139	85	2568	
Male	100%	100%	1.00	100%	57.7%	56.5%	<.0001
Age at Diagnosis, yr (median)	14.4±2.3	14.6±2.0	.962	14.4±2.3	10.2±4.8	5.3±6.0	<.0001
	(14.9)	(14.5)		(14.8)	(10.2)	(1.7)	
Race			.060				<.0001
White	74.6	53.3		72.3	90.5	60.6	
Black	13.9	20.0		14.6	2.4	16.7	
Hispanic	9.8	13.3		10.2	7.1	16.5	
Other	1.6	13.3		2.9	0.0	6.2	
CHF at Diagnosis	30.1	33.3	.773	30.4	11.9	51.0	<.0001
Type of Cardiomyopathy			1.00				<.0001
Hypertrophic	0.0	0.0		0.0	79.8	32.5	
Dilated	96.8	100		97.1	14.3	55.3	
Restrictive	0	0		0.0	0.0	3.4	
Other and Mixed Type	3.2	0		4.9	6.0	8.8	
Functional Class (NYHA or Canadian Criteria)			.347				<.0001
I (Includes asymptomatic pts)	78.4	66.7		77.0	90.4	63.4	
II	9.9	20.0		11.1	3.6	6.9	
III	7.2	13.3		7.9	3.6	10.9	
IV	4.5	0.0		4.0	2.4	18.8	
Anticongestive Therapy	67.8	60.0	.568	66.9	20.0	60.9	<.0001
Antiarrhythmic Therapy	20.6	33.3	.602	22.5	10.8	26.3	.098
ACE Inhibitor	38.2	33.3	1.00	37.5	8.1	42.7	.0001
Ca ++ Channel Blocker	2.9	0	1.00	2.5	8.3	6.7	.525
Beta-adrenergic receptor	0	0	-	0.0	5.6	10.9	.054
Family History of CM	9.2	0.0	.596	8.3	9.7	18.5	.003
Family History of Sudden Death	1.8	0.0	1.00	1.6	3.9	8.2	.013
Family History of Genetic Syndromes	25.0	0.0	.068	22.8	14.9	3.5	<.0001
Family History of Congenital Heart Disease	0.0	0.0	-	0.0	0.0	4.9	.008
Family History of Arrhythmia	0.9	0.0	1.00	0.9	7.0	2.7	.038

Table 2. Estimated Time to Death (years)

Group	Percentile	Estimate	95% CI
DMD	25	2.2	(1.7, 3.2)
	50	5.4	(4.1, 8.1)
BMD	25	-	-
	50	-	-
DMD + BMD	25	2.4	(1.8, 3.8)
	50	5.7	(4.5, 8.1)
Other NM Disease	25	-	-
	50	-	-
Non-NM Disease	25	10.3	(7.3, -)
	50	-	-

Table 3. Estimated Time to Death or Transplant (years)

Group	Percentile	Estimate	95% CI
DMD	25	2.2	(1.7, 3.2)
	50	5.4	(4.1, 8.1)
BMD	25	0.4	(0.1, -)
	50	-	-
DMD + BMD	25	2.4	(1.8, 3.8)
	50	5.7	(4.5, 8.1)
Other NM Disease	25	9.6	(6.6, -)
	50	-	-
Non-NM Disease	25	0.8	(0.6, 1.0)
	50	11.5	(10.3, -)

Table 4. Echocardiographic Characteristics at Diagnosis by Etiology

Characteristic	DMD	BMD	DMD vs. BMD p-value	DMD + BMD	Other NM Disease	Non-NM or Idiopathic Disease	p-value
N for echo data	123	15		138	82	2467	
Mitral regurgitation*			.093/.048				.001
None	55.9	16.7		50.0	80.0	43.9	
Mild	26.5	33.3		27.5	20.0	36.1	
Moderate	17.7	50.0		22.5	0.0	16.6	
Severe	0.0	0.0		0.0	0.0	3.4	
LV EDD z-score	1.16±1.88	2.94±1.50	.003	1.39±1.92	-0.32±2.27	1.99±4.14	<.0001
LV ESD z-score	2.63±2.31	4.47±2.18	.024	2.85±2.36	-0.93±3.35	2.72±5.34	<.0001
Fractional shortening z-score	-5.38±3.22	-6.64±3.70	.335	-5.50±3.27	1.17±5.39	-4.28±7.04	<.0001
End-diastolic posterior wall thickness z-score	-1.72±2.23	-1.94±2.17	.957	-1.75±2.21	2.52±2.32	0.64±3.07	<.0001
End-diastolic septal wall thickness z-score	-1.40±1.38	-1.76±2.65	.949	-1.44±1.57	2.43±1.89	1.01±2.99	<.0001
LV mass z-score	-0.53±1.83	-0.39±1.54	.064	-0.42±1.81	2.21±1.89	2.14±2.94	<.0001

*First p-value is chi-square or exact test and second is test for linear trend.

Figure 1: DMD (N=124) vs. BMD (N=15) vs. Other NM (N=85) vs. Non-NM (N=2568)
SURVIVAL-PCMR DATABASE DECEMBER 2003

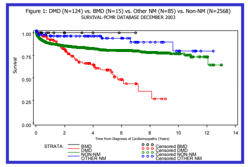
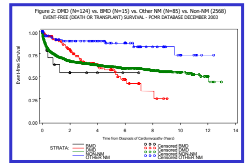


Figure 2: DMD (N=124) vs. BMD (N=15) vs. Other NM (N=85) vs. Non-NM (2568)
EVENT-FREE (DEATH OR TRANSPLANT) SURVIVAL - PCMR DATABASE DECEMBER 2003



CONCLUSIONS

- At the time of CM diagnosis patients with BMD trend (p=.093) to have mitral regurgitation (83% vs. 44%), and a higher LV end diastolic dimension (2.9 vs. 1.2 BSA-adjusted Z-score, p=.003) than patients with DMD (Table 4).
- Following diagnosis for CM, DMD patients have a higher mortality rate and BMD patients may have a higher transplant rate than pediatric patients with other types of CM Tables 2 & 3).
- There is a more rapid short-term decline in event-free survival after diagnosis in BMD patients than in DMD patients (Table 3).
- β-blockers are not commonly used in DMD/BMD patients even in the presence of heart failure symptoms and abnormal functional class (Table 1).
- DMD/BMD patients present with echocardiographic criteria of CM at a later age than patients with other pediatric cardiomyopathies (Table 1).

LIMITATIONS

- This is a combined retrospective/prospective study with data obtained by chart review. While data collection was standardized, not all data were present on all subjects.
- Echocardiographic data was obtained using varying measurement techniques and echocardiographic equipment in each center. Data were collected from report forms. No central review of echocardiographic images was performed.
- Only patients who were diagnosed as having clinical cardiomyopathy by PCMR criteria were enrolled in this study. It is therefore not possible to follow the progression of disease prior to meeting these criteria, even though it is known that the process leading to clinical cardiomyopathy begins prior to this point.
- Comparisons to BMD cohort may have low statistical power due to the small size of this cohort.

REFERENCES

[i] Beggs AH. Dystrophinopathy, the expanding phenotype: Dystrophin abnormalities in X-linked dilated cardiomyopathy. Circulation 1997;95(10):2344-2347.

[ii] Towbin JA, Hejtmancik JF, Brink P, Gelb B, Zhu XM, Chamberlain JS, McCabe ER, Swift M. X-linked dilated cardiomyopathy. Molecular genetic evidence of linkage to the Duchenne muscular dystrophy (dystrophin) gene at the Xp21 locus. Circulation. 1993 Jun;87(6):1854-65.

[iii] Manning GW and Cropp GJ. The electrocardiogram in progressive muscular dystrophy. Br Heart J 1958;20:416-420.

[iv] Nigro G, Comi LI, Politano L and Bain RJI. The incidence and evolution of cardiomyopathy in Duchenne muscular Dystrophy. Int J Cardiol 1990;26:271-277.

[v] Finsterer J, Stollberger C. The heart in human dystrophinopathies. Cardiology. 2003;99(1):1-19.

[vi] Nigro G, Comi LI, Politano L, Limongelli FM, Nigro V, De Rimini ML, Giugliano MA, Petretta VR, Passamano L, Restucci B, et al. Evaluation of the cardiomyopathy in Becker muscular dystrophy.Muscle Nerve. 1995 Mar;18(3):283-91.

[vii] Simonds A, Muntini F, Heather S and Fielding S. Impact of nasal ventilation on survival in hypercapneic Duchenne muscular dystrophy. Thorax 1998;53(11):949-952.

[viii] Ishikawa Y, Bach JR, Ishikawa Y, Minami R. A management trial for Duchenne cardiomyopathy.Am J Phys Med Rehabil. 1995 Sep-Oct;74(5):345-50.

[ix] Ishikawa Y, Bach JR, Minami R. Cardioprotection for Duchenne's muscular dystrophy. Am Heart J. 1999 May;137(5):895-902.

[x] Melacini P, Vianello A, Villanova C, Fanin M, Miorin M, Angelini C and Dalla Volta S. Cardiac and respiratory involvement in advanced stage Duchenne muscular dystrophy. Neuromusc Disor 1996;6(5):367-376.

[xi] Grenier MA, Osganian SK, Cox GF, Towbin JA, Colan SD, Lurie PR, Sleeper LA, Orav EJ, Lipshultz SE. Design and implementation of the North American Pediatric Cardiomyopathy Registry. Am Heart J. 2000 Feb;139(2 Pt 3):S86-95.