Left Ventricular Dysfunction in Duchenne Muscular Dystrophy and Genotype

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Prognosis in patients with Duchenne muscular dystrophy (DMD) is guarded, and most deaths are due to cardiac or respiratory causes. It is unclear if some *DMD* gene mutations might be predictive of either mild or severe cardiac dysfunction. We studied 75 patients with DMD followed at our institution. Cardiac function, as assessed by yearly echocardiography, showed marked variability in left ventricular (LV) function. Some patients in their 3rd decade had no or minimal dysfunction, whereas others in their 2nd decade had very severe dysfunction. Therefore, 4 severity groups were defined ranging from no or mild LV dysfunction to severe LV dysfunction using patient age at first abnormal echocardiographic finding and degree of LV dysfunction. Genetic data were collected for all patients. Most patients had mutations from exon 1 to 20 to exon 41 to 55. The distribution of the 4 severity groups of LV dysfunction did not significantly differ between these 2 mutation groups. An analysis based on the number of exons involved (<5 vs ≥5 exons) also found no significant difference in cardiac severity. When patients having identical mutations were compared with their cardiac course, concordance was often not evident. Steroid therapy had no apparent protection for the development of cardiomyopathy. In conclusion, 75 patients with DMD showed marked variability in the severity of LV dysfunction. Neither the age of onset nor the severity of cardiomyopathy correlated with any of the mutation groups. **(Am J Cardiol 2014;114:284−289)**

Duchenne muscular dystrophy (DMD) results in skeletal and cardiac muscle dysfunction and is caused by mutations in the *DMD* gene located at Xp21.1.[1] Most mutations are deletions[2−4] and result in the absence or minimal amounts of dystrophin, a subsarcolemmal protein product first identified in 1987.[5] As a consequence, cardiac dysfunction and respiratory muscle weakness develop and often result in premature death in the 2nd or 3rd decade of life.[6] Most patients develop myocardial disease characterized by early and extensive fibrosis in the basal inferolateral wall of the left ventricle (LV) and, later, the lateral free wall.[7−10] Although cardiomyopathy develops in at least 90% of patients, the age when this becomes clinically evident is variable.[11−13] Several previous reports suggested that some *DMD* mutations might be predictive of more severe cardiac involvement[13] and some mutations might be cardioprotective.[14] However, no study has specifically focused on characterizing the marked variability in onset and severity of LV dysfunction and whether this variability is predictable by genotype. The clinical implications of such correlations would be significant with the potential of a specific genotype predicting patients at either high or low risk of early LV dysfunction. Conversely, absence of any correlation would not allow predictions of risk.

Methods

Patients (n = 124) with a dystrophinopathy who were followed in the MetroHealth Medical Center Muscular Dystrophy Association Clinic over the years 1999 to 2011 were eligible for inclusion in the study. Patients with DMD and Becker muscular dystrophy have similar *DMD* mutations, and patients with Becker muscular dystrophy often develop severe cardiac dysfunction. Nevertheless, those with Becker muscular dystrophy were excluded from the present study leaving 104 patients having DMD, none of whom were walking at 12 years of age. Additional exclusion criteria were age <10 years at their last visit or inadequate echocardiographic data. The remaining 75 patients with DMD are the focus of this study. Demographic and clinical data including age, race, and the genetic mutation were collected for all the patients. The hospital's Institutional Review Board approved the study.

Cardiac function was assessed by echocardiography. One coauthor (MLA), blinded to the specific genotype, reevaluated and measured all echocardiograms to obviate interobserver variability. Standard cardiac imaging was performed using either Philips Sonos 500 or Philips iE33 (Andover, Massachusetts) imaging systems and repeated at approximately yearly intervals. Images were stored in a digital format. The LV internal dimension at end-diastole and the LV internal diameter at end-systole were measured from the

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See page 289 for disclosure information.

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Table 1
Severity groups as related to patient age and degree of left ventricular dysfunction

Severity Group	Age	Degree of Left Ventricular Dysfunction
1	≥15	None
1	>19	Minor
2	<15	None
2	15−19	Minor
3	<15	Minor
3	>19	Major
4	≤19	Major

Table 2
Patient characteristics (n = 75)

Race	
European American	70 (93%)
African American	3 (4%)
Hispanic	2 (3%)
Mutation type	
Deletion	54 (72%)
Duplication	14 (19%)
Nonsense	4 (5%)
Frame shift	2 (3%)
Splice site	1 (1%)
Medication usage	
ACE-inhibitor*	45 (60%)
Angiotensin receptor blocker*	3 (4%)
Beta-blocker*	26 (35%)
Digoxin*	18 (24%)
Steroid	11 (15%)
Location of mutations	
Group A (exon 1−20)	22 (29%)
Group B (exon 21−40)	3 (4%)
Group C (exon 41−55)	46 (61%)
Group D (exon >55)	4 (5%)
Number of mutations	
Group L5E (<5 exons)	47 (63%)
Group G5E (≥5 exons)	28 (37%)
Severity of cardiomyopathy	
Severity group 1	31 (41%)
Severity group 2	10 (13%)
Severity group 3	21 (28%)
Severity group 4	13 (17%)

* Initiated after evidence of LV dysfunction.

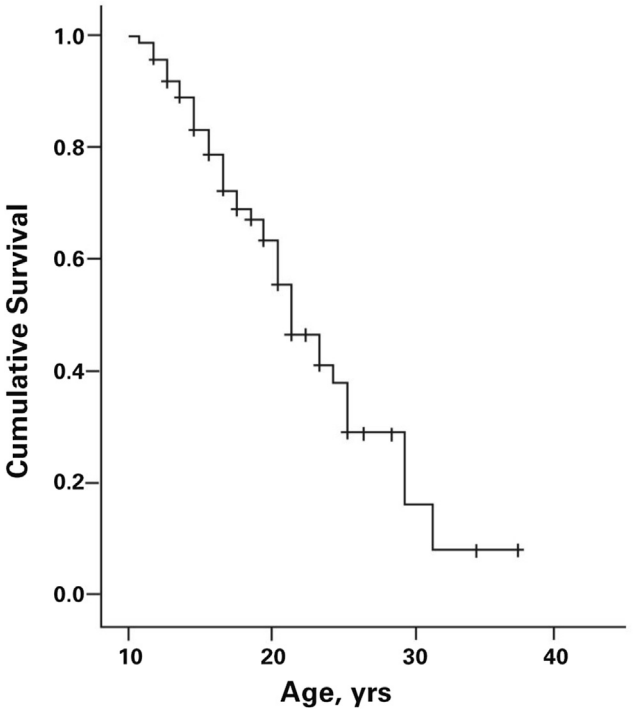

Figure 1. Cumulative survival rates without echocardiographic evidence of cardiomyopathy as related to age. Note that not all patients with DMD have echocardiographic evidence of cardiomyopathy at the age of 25 years.

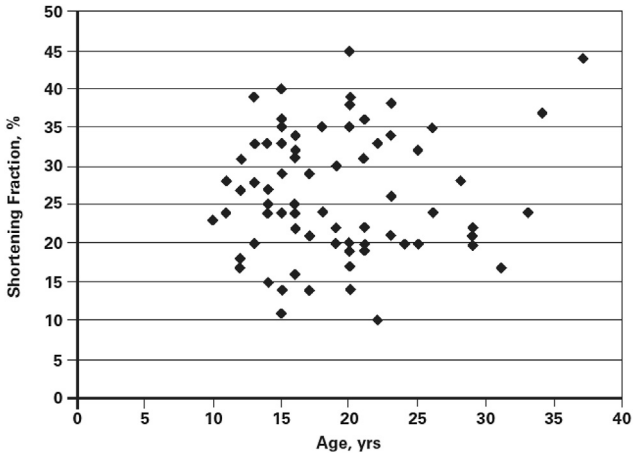

Figure 2. SF as related to patient's age. The patient's age at their last normal echocardiographic finding is displayed for those patients with a persistently normal SF (SF ≥29). When patients had an abnormal SF, the age at the first abnormal SF is displayed. The distribution of patients with either normal SF or abnormal SF is unrelated to age. The variability of SF is marked.

2-dimensional parasternal long-axis view. End-diastole was defined as the largest diameter before the onset of shortening so as to avoid the diastolic compression of the posterolateral wall from gastric pressure. Three cardiac cycles were measured for each study, and the mean values were used to calculate the LV shortening fraction (SF) expressed as a percentage: {[(LV internal dimension at end-diastole − LV internal diameter at end-systole)/LV internal dimension at end-diastole] × 100}.

Although cardiomyopathy may be evident by measurements of circumferential strain, tissue backscatter, and myocardial tissue velocities before reductions in ejection fraction or SF,[15−17] we considered LV dysfunction and cardiomyopathy to be present only if the SF was <29% and focal hypokinesia was present. SF rather than ejection fraction was chosen for the serial observations because (1) ejection fraction is best calculated from apical images, but the quality of apical images in patients with DMD markedly deteriorates with increasing age because of loss of intercostal windows and (2) SF incorporates the function of the basilar inferolateral wall, which is the earliest and dominant region of LV dysfunction in almost all patients; thus, the SF may be reduced when the LV ejection fraction is normal.