Prognostic Effect Of Convertional Treatment In Pediatric Dilated Cardiomyopathy

Pediatrik Dilate Kardiyomiyopatide Medikal Tedavinin Prognoza Etkisi

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Abstract

The purpose of this study was to review our experience with conventional treated pediatric dilated caridomyopathy patients in our region and attempt to discover prognostic factors. We analyzed retrospectively the outcome of 41 patients during last six years. The patients were 23 girls, and 18 boys, ejection fraction 31.6±7.8%, follow-up period 14.07±14.2 months. Eight patients (19.5%) had died, 17 (41.4%) had recovery of systolic function. When analyzed from regained normal systolic function (17 patients) and others, first ejection fraction was not statistically significant (p=0.743). When separated from patient presentation age, 58.5% were smaller than two years. Sixth patients (25%) were died in smaller and two (11.7%) in bigger. Comparison between groups were not statistically differences (p=0.632 for deaths, p=0.594 for ejection fraction). We concluded that age; degrees of systolic functions were not differentiated favorable outcomes.

Key words: Dilated cardiomyopathy, Prognosis, Childhood

Özet

Pediatrik dilate kardiyomiyopatili hastalarımızda konvensiyonel tedavide prognoza etki eden faktörleri araştırmayı planladık. Son altı yıl içinde hastanemizde tedavi edilen 41 dilate kardiyomiyopatili çocuk hastanın retrospektif değerlendirmesi yapıldı. 23 kız, 18 erkek, başlangıç ejeksiyon fraksiyonu ortalama %31.6±7.8, izlem süresi ise 14.0±14.2 ay idi. İzlemde 8 hasta (%19.5) öldü, 17 hastanın (%41.4) sistolik fonksiyonu zamanla düzeldi. Sistolik fonksiyonu düzelen hastaların başlangıç ejeksiyon fraksiyon değerleri düzelmeyenlere göre istatistiksel olarak anlamlı değildi (p=0.743). Başvuru yaşlarına göre hastalar iki gruba ayrıldığında %58.5 hasta iki yaştan küçüktü. İki yaştan küçük hastalardan altısı (%25), iki yaştan büyüklerden ise ikisi (%11.7) öldü. Grupların karşılaştırılması istatistiksel olarak anlamlı bir fark vermedi (p=0.632). Hastalığın başlangıç yaşı ve sistolik fonksiyonun başlangıç değerinin hastalık prognozunu göstermede etkin olmadığını düşünmekteyiz.

Anahtar Kelimeler: Dilate kardiyomiyopati, Prognoz, Çocukluk çağı

Introduction

Pediatric dilated cardiomyopathy is a cardiac muscle disease of an undefined etiology characterized by global hypokinesia of the ventricles resulting symptoms of heart failure in children. It accounts for only 1% of pediatric cardiac disease but can lead to significant morbidity and death (1,2). Despite an intensive search for causes using the most advanced molecular methods, the majority of cases have to designate as idiopathic. The clinical and hemodynamic outcomes of patients with idiopathic dilated cardiomyopathy are highly variable. The long-term prognosis for children with recovered dilated cardiomyopathy remains uncertain. This study provides data on the prognosis of children with dilated cardiomyopathy treated with conventional management with a retrospective analysis of data about six years.

Methods and Patients

Patient characteristics: The database of our echocardiography units was searched for all children with the diagnosis of dilated cardiomyopathy between July 1999 and August 2005. Medical records were reviewed to document clinical presentation, including symptoms, primary diagnosis, presence of arrhythmia, and a positive family history. Exclusion criteria included patients who have congenital heart diseases, arrhythmogenic cardiomyopathy, using of an antineoplastic drug, rheumatic heart disease, neuromuscular disease, blood disorders, systemic arterial hypertension, chronic renal failure. Patients with a clinical diagnosis of myocarditis could not exclude from the study.

Echocardiographic studies: Each patient was examined in a supine position by using a GE Vingmed ultrasonography with 2.5 and 3.5 MHz transducers.

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Echocardiograms were analyzed for ejection fraction, fractional shortening, mitral valve insufficiency, left ventricular end-diastolic and end-systolic dimensions, and left ventricular end-diastolic and end-systolic volumes. All patients were assessed at baseline and subsequently every three months during the study interval. All the measurements were taken by the same two investigators. Impaired myocardial function was described that left ventricular ejection fraction of<50%. Left ventricular ejection fraction was the primary echocardiographic variable in assessing ventricular function in patients with dilated cardiomyopathy.

Other laboratory studies: Holter monitors and 12-lead electrocardiograms were also examined for evidence of arrhythmia. Other laboratory studies included chest radiographs, serum carnitine and plasma amino acids and urine organic acids in selected infants for metabolic screens.

Follow-up: Patients were scheduled for follow-up visits every three months and were encouraged to schedule additional visits if any clinical problems had occurred.

Medical treatment: Therapy for heart failure was standardized in that all patients were administered angiotensin converting enzyme inhibitors, digitalis, diuretics, and oral anticoagulants if it is necessary. Some patients with in severe heart failure treated with a beta-adrenergic blocking agent. Addition, in severe heart failure, intravenous inotropic support was given. Patients with unresponsive to the therapy were given corticosteroids or immunoglobulin.

Outcome: Death and improvement of left ventricular systolic function were primary outcomes of interest.

Statistical analysis: Descriptive statistics are expressed as mean±SD. Paired t-test was used to compare intergroup data. Chi square was used in the case of discrete variables. Survival analysis was assessed by using Kaplan Meier analysis. A p value <0.05 was considered significant. The analyses were performed using the Statistical Package for the Social Sciences 11.0 (SPSS, Inc., Chicago, IL, USA) for Windows computer program.

Results

Totally, 144 patients had left ventricular dilatation during the study period. Excluding secondary causes and lost of follow-up, analysis included 41 patients (23 girls, 56.1% and 18 boys, 43.9%, aged ranged of 0.16-15, mean 2.65±3.53, and median one year). All patients presented with clinical signs of congestive heart failure. One patient had a family history suggestive of familial cardiomyopathy. Six patients were thought to have myocarditis. One patient had left hemiparalysis because of embolic phenomena, one another was given intravenous heparin because of thrombus in the left ventricular cavity. One patient with acquired complete atrioventricular block had needed transvenous pacemaker therapy. Except conventional therapy, therapies of six patients were done with beta-blockers, corticosteroids and/or intravenous immunoglobulin.

Table 1. Comparison between group N (patients who had improvement in their systolic functions) and group X (patients who dead or had persistent left ventricular dysfunction).

	Group N (n=17)	Group X (n=24)	p
Age (years)	2.58±3.7	2.69±3.4	0.927
Sex	8 F, 9 M	15 F, 9 M	
LVDd at presentation (cm)	4.06±0.7	4.53±0.9	0.088
LVDs at presentation (cm)	3.44±0.6	3.83±0.7	0.106
LVVd at presentation (ml)	76.40±30.4	99.40±45.7	0.064
LVVs at presentation (ml)	51.67±21.8	65.68±32.2	0.114
EF at presentation (%)	32.17±8.3	31.33±7.5	0.743
FS at presentation (%)	15.74±4.4	15.26±4.4	0.738
Mitral insufficiency at presentation	1.76±0.8	2.54±0.6	0.003*
Follow-up time	17.32±14.0	11.77±14.2	0.224
LVDd at last follow-up (cm)	3.57±0.5	4.52±1.1	0.002*
LVDs at last follow-up (cm)	2.50±0.4	3.75±0.9	0.000*
LVVd at last follow-up (cm)	53.67±19.9	103.86±58.7	0.001*
LVVs at last follow-up (cm)	23.10±9.4	67.03±40.1	0.000*
EF at last follow-up (%)	58.58±3.7	34.04±12.2	0.000*
FS at last follow-up (%)	30.31±2.3	16.28±6.6	0.000*
Visit number	6.12±3.4	5.25±3.9	0.453

(F; female, M; male, LVDd; left ventricular end-diastolic dimensions, LVDs; left ventricular end-systolic dimensions, LVVd; left ventricular end-diastolic volumes; LVVs; left ventricular end-systolic volumes, EF; ejection fraction, FS; fractional shortening, *; statistically significant).

Table 2. Comparison between group S (<2 years) and B (>2 years).

	Group S (n=24)	Group B (n=17)	c^2	p
Age (year)	0.62±0.33	5.51±4.01		0.000*
Sex	12 F, 12 M	11 F, 6 M		
Death number	6	2	0.228	0.632
EF at presentation (%)	31.12±7.8	32.47±7.9		0.594
FS at presentation (%)	15.24±4.5	15.77±4.3		0.704
Mitral insufficiency at presentation	2.08±0.8	2.41±0.6		0.169
Follow-up time	16.97±16.9	9.97±8.1		0.087
EF at last follow-up (%)	42.54±17.7	46.58±11.9		0.389
FS at last follow-up (%)	21.27±9.7	23.26±7.1		0.457
Visit number	6.33±4.4	4.59±1.9		0.096

(F; female, M; male, EF; ejection fraction, FS; fractional shortening, *; statistically significant)

The overall follow-up period ranged form 14 days to 62 months (mean 14.07±14.2 months). The mean left ventricular end-diastolic dimension was 4.34±0.87 cm, and end-systolic dimension 3.67±0.76 cm, ejection fraction 31.6±7.8% and fractional shortening 15.4±4.4%. At the follow-up, left ventricular systolic functions were improved by the time (Figure 1.)

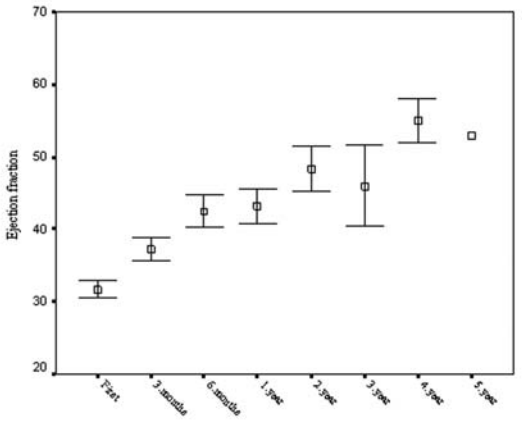

Figure 1. Ejection fraction changing with follow-up time (mean ± standard error).

During follow-up eight patients (19.5%) died with of cardiac causes. Survival time was mean 47.9, standard error 4.6 months (95% CI:39.0-56.8) (Figure 2). The majority of deaths (75%) occurred within the first 3.5 months. The two late deaths occurred within eight and 26 month after presentation. In the left 33 survivors, 17 (41.4%) regained normal left ventricular dysfunction (ejection fraction>55%), 16 (39%) had persistent left ventricular dysfunction.

We firstly separated two groups' patients with regarding regained normal left ventricular function (Group N) and persistent left ventricular function and death patients (Group X). Group N included 17 patients (nine boys, eight girls, mean age 2.58±3.7 years) and Group X 24 patients (nine boys, 15 girls, and mean age 2.69±3.4 years).

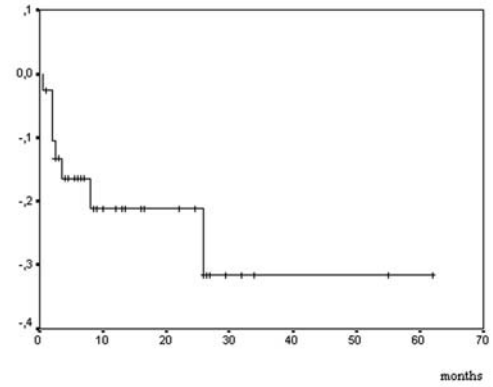

Figure 2. The overall survival curve of children with dilated cardiomyopathy (logarithmic survival function was shown, survival function, + censored patients).

Comparison between group N and X was not statistically differences between fist presentation ejection fraction and fractional shortening (Figure 3 and Table 1). Mitral valve insufficiency was only statistically difference at the first presentation between groups.

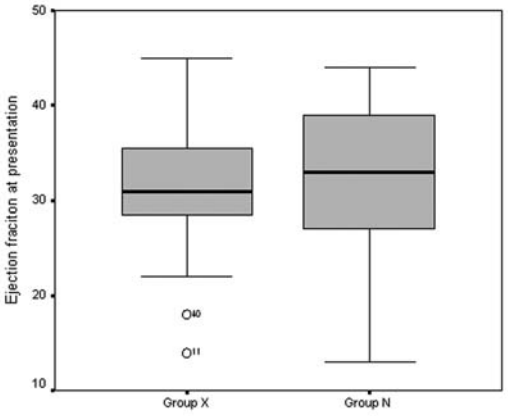

Figure 3. Ejection fraction at presentation between groups X (patients who dead or had persistent left ventricular dysfunction) and group N (patients who had improvement their in).

Regarding patient age, 24 patients (58.5%) were smaller than two years (Group S), 17 patients (41.5%) bigger than two years (Group B). Sixth deaths were happened in group S (25%) and two deaths in group B (11.7%). Comparison between groups regarding deaths and degree of left ventricular systolic functions were not statistically differences (Table 2).

All parameters were assessed by multivariate analysis and separately by univariate analysis to determine their association with outcome. Degree of mitral insufficiency at presentation was associated with outcome by multivariate analysis (Table 3). Univariate analysis of mitral insufficiency was improvement left ventricular function (mitral insufficiency mean 1.76±0.83) versus unchanged or worsened patients (mean 2.44±063) and dead patients (mean 2.75±0.46) (F=6.706, p=0.003).

Discussion

Multiple reasons including infection, mutations of myocardial cytoskeleton and structural proteins, and disorders of myocardial metabolism can cause pediatric dilated cardiomyopathy. Although most cases of pediatric dilated cardiomyopathy are idiopathic, diagnostic algorithms (3) have increased the proportion of pediatric dilated cardiomyopathy cases with a known cause. Felker et al (4) demonstrated that rigorous and systemic search could show underlying cause for approximately one-half of patients with unexplained cardiomyopathy in adults. The most common histologic diagnosis in dilated cardiomyopathy was shown as myocarditis (4). But this trend is not reflected in our study because of some technical limitations like not performed endomyocardial biopsy. So, previously or active myocarditis could not be excluded in patients with dilated cardiomyopathy. Diagnosis of myocarditis was established only clinical presentation with viral studies and coexistent symptoms. Of course, myocarditis can recover spontaneously and furthermore the presence of a virus does not necessarily establish a causal relationship.

In the present study, the median age was 12 months. Similar results were reported in some studies (5,6), although some authors reported more smaller age (7,8). In a large study in Australia, Nugent et al (7) found that the median age at presentation was 7.5 months among children with dilated cardiomyopathy.

The overall outcome of the patients was poor; 19.5% of them died. Venugopalan et al (9) also reported that 19% death rates. Grenier et al (1) reported similar survival rates (15%) in patients who diagnosed from 1990 to 1995, although the same authors more favorable outcomes (11%) reported in patients who diagnosed from 1996 to 1998. Addition outcome seems to improve over time in the reported studies (1,5,10,11). Nugent et al (7) demonstrated that death was the presenting symptoms in 4.9% rates. The differences in outcome may be explained partly by differences inclusion myocarditis, as well as by the relatively small population in our study.

Furthermore, we could not use a transplantation choice in our patient because of technical problems. Predictors of adverse clinical outcomes among children with dilated cardiomyopathy remain incompletely defined (6,12,13). Degree of depression of fractional shortening or ejection fraction at time of initial echocardiography, elevation of left ventricular end diastolic pressure, and cardiothoracic ratio have all been applied as predictors of outcome, although they are not often predictive (14) Other possible prognostic factors include age at onset, presence of symptomatic arrhythmias, and thromboembolic episodes (5,6,15,16). Age at presentation has been a strong prognostic indicator in some earlier studies (6,16), whereas other reports have found no difference in outcome between children before and after two years of age (5,15). A large retrospective study showed by multivariate analysis that young age presentation was associated with improved survival and by univariate analysis that age of presentation of after two years of age was associated with poor prognosis (6). But, age of presentation was not a statistically significant predictor of outcome in the present study. Also we found not in a connection ejection fraction, fractional shortening, left ventricular end-diastolic and end-systolic dimensions and other parameters except mitral valve insufficiency between favorable outcomes.

In our population, 41.4% of patients had an improvement in the left ventricular systolic function. It has been reported that a spontaneous recovery in the left ventricular function can be observed in down to 19% in adults (17). Included patients with dilated cardiomyopathy in our study might have more myocarditis than we thought, and our patient population was children. Potential of recovering of left ventricular systolic function in children might be bigger than adults.

The current treatment for severe clinical pictures of cardiomyopathy is usually heart transplantation (16). A significant number of children with dilated cardiomyopathy may develop end-stage heart failure that requires cardiac transplantation. This is an unrealistic option for the developing world. The management strategy of childhood dilated cardiomyopathy in the developing world needs to be tailored to the resources available with in a manner such that the overall prognosis is not substantially affected. Several studies show that stem cells can be isolated, amplified in culture, and manipulated to differentiate into cardiomyocytes (18). In addition, a recent report indicates that zebrafish myocardium can regenerate (19) we come to understand the mechanisms that allow the regulation of regeneration in myocardium, treatment through the induction of regeneration may prove feasible, especially in patients with postinfectious and toxic cardiomyopathy.

The present study is limited by its retrospective design. So, the number of variables for prognostic predictor was necessarily limited. Occult disease might be not referred in our center. It was possible that severe clinical pictures were more included in our study.

We concluded that age, degree of ejection fraction and fractional shortening at presentation were not differentiated favorable outcomes. We believed that to improve the total care of patients at the beginning of disease (especially first 3-4 months) and the use of transplantation choice were important in improving the quality of life.

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