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Idiopathic dilated cardiomyopathy in children;
Natural history and predictors of prognosis

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Abstract: Dilated cardiomyopathy is the most common type of heart muscle disease in children with idiopathic etiology in the majority of cases. Idiopathic dilated cardiomyopathy (IDCM) is a severe illness which carries a high mortality rate in the pediatric population. In order to characterize IDCM evolution and identify prognostic predictors in our pediatric cardiology center in the western province of Saudi Arabia, 55 patients with IDCM were evaluated clinically and by echocardiography. They were followed for a minimum of one year and a maximum of four and a half years. Patients less than two years of age represented 69% of the cohort. Gender distribution revealed 65.5% female and 35.5% male. Outcomes were divided into four groups: 25 patients (45.5%) improved (Group I), 17 patients (31%) had a stationary course (Group II), 13 patients (23.6%) deteriorated (Group III), and eventually 11 patients (from Group III) died. Survival rate was 80% with a mean follow-up period of 36.2 ± 22.1 months. The older the age at presentation, the worse the prognosis, with P value= 0.029. In this study, we found a significant correlation of prognosis with end diastolic volume (EDV) (P=0.05) as well as stroke volume (SV) (P=0.04) on presentation. However, fractional shortening of ejection fraction on presentation could not be correlated statistically to the prognosis. Also results suggested that higher z-score of intraventricular septum & Left ventricular posterior wall dimensions in diastole significantly correlated to favorable outcomes and higher z-score of Left ventricular end diastolic dimension (LVEDD) was significantly related to unfavorable outcome. We concluded that further multi-center studies are necessary to verify predictors of outcome in IDCM patients. Identification of markers affecting early myocardial function is essential to achieving improvements in treatments and consequently outcomes in this pediatric population.

Key Words: *dilated cardiomyopathy, children, natural history, predictors of prognosis, echocardiography*

Introduction

Dilated cardiomyopathy is a heterogeneous group of myocardial diseases characterized by cardiac dilatation and impaired myocardial contractility [1]. DCM is an uncommon disease in children but morbidity and mortality in affected patients are high [2]. However, a high degree of variability has been observed in the clinical course and in the morphologic as well as hemodynamic features. Despite an intensive search for the cause using the most advanced molecular methods, the majority of cases (66%) remain designated as idiopathic [3-5]. The incidence of cardiomyopathy in infants and children is difficult to assess, in part because of the variation in diagnostic criteria in different regions of the world and partly because of the heterogeneous etiologies of the disease [6].

Arola reported in Finland the annual incidence of idiopathic dilated cardiomyopathy (IDCM) in children to be 0.34 cases per 100.000 of the age-specific population [4]. An annual incidence of 1.24 per 100,000 children younger than age ten for all types of cardiomyopathy (dilated, hypertrophic and restrictive) was reported in Australia [7]. In a multi-centre study carried out in the USA, the incidence of DCM in children <18 years was 0.57 cases per 100 000 per year [5]. In DCM, the prognosis is often poor irrespective of etiology [8], with a reported five-year mortality of up to 80% in IDCM patients in some series [4], Studies from 1975-90 reported 70% survival at two years and 52% survival at 11.5 years. Studies from 1992-97 have reported up to 85% survival at five years [9-12]. DCM is the most common cause for pediatric

cardiac transplantation in children [13]. Although heart transplantation is increasingly used to treat this population, selection of patients and timing of the procedure remain problematic [4]. Operative complications as well as post-operative morbidities are considerable; nonetheless worldwide availability of such highly specialized surgeries is questionable [14]. The clinical course of the disease is often unpredictable in the individual patient [15] which suggests the need to establish an optimal management plan and define predictors of prognosis more accurately.

Aim of the Study

To determine the outcome of children and adolescents with idiopathic dilated cardiomyopathy (IDCM) and to evaluate echocardiographic indicators that may prove helpful in predicting prognosis in this patient population.

Subject and Methods

A prospective, clinical observational study was planned. All patients presented with the diagnosis of idiopathic dilated cardiomyopathy (IDCM) in the pediatric cardiology center-Al Noor Specialist Hospital (a tertiary care hospital in Makkah-KSA).

The study was performed over four and a half years from June 2001- December 2005.

Patients included in this study were followed for a period of one to four and a half years with a mean of 36.2 ± 22.1 months.

Inclusion Criteria

The left ventricular end-diastolic dimension (LVEDD) ≥ 2 SD units above normal according to the body surface area of the patient, Ejection fraction (EF) was required to be ≤ 50% and fractional shortening (FS) had to be 25% [12].

Exclusion Creteria

Transient cardiac abnormalities (e.g., acute myocarditis), patients were included only if their cardiac size or function, or both, remained abnormal for at least 6 months. Patients diagnosed with secondary forms of myocardial disease were also excluded.

There were in total 80 patients diagnosed with DCM. In 25 (roughly 31 %) a cause was found: Causes of secondary DCM in these patients were: anomalous LCA origin (diagnosed by cardiac catheterization), sepsis, severe peri-natal hypoxia, post diphtheria, uremia, coarctation and metabolic diseases.

Fifty-five patients had idiopathic dilated cardiomyopathy (IDCM). Ages ranged from 1 month -11 years with a median of 12 ± 37.4 SD months. Females represented 65.5% of the study group.

For all patients our evaluation consisted of the following:

On presentation: A full history was taken on each patient. Clinical examination included: ECG- Chest X ray - Echocardiography using M and 2 D modes, Doppler and color Doppler using General Electric medical echocardiographic machine (model: vived 7 Pro, GE Vingmed ultrasound AS-N190, Horton-Norway equipped with 3,7 &12 MHZ transducers).

By echocardiography M-Mode, the following measures were taken: Interventricular septum in diastole & systole (IVSd & IVSs), Left ventricular dimension in diastole& systole (LVEDd & LVEDs), Left ventricle posterior wall in diastole & systole (LVPd & LVPs). End diastolic volume (EDV), End systolic volume (ESV), Stroke volume (SV), Fractional shortening (FS) and Ejection fraction (EF) were obtained digitally. Z-score of echocardiographic measures on presentation was calculated [16].

Therapy

All patients received diuretics, angiotensin-converting enzyme (ACE) inhibitors, and digoxin with Aspirin (prophylactic dose) as initial therapy. Patients were admitted to the hospital for IV inotropes if they deteriorated clinically. Anti-arrythmic drugs were used if arrhythmias occurred.

Follow-up visits were scheduled at one to three month intervals according to patient condition and during each visit a full clinical examination, ECG, chest X-ray and echocardiography were completed.

Grouping

According to outcomes, patients were divided into three groups.

Group I consisted of patients who improved, Group II had a stationary course, and Group III were those patients who deteriorated (both clinically and echocardiographically) and/ or died. Improvement was defined as an asymptomatic situation with left ventricular dimensions and function having returned to normal. Patients with a stationary course were asymptomatic or had mild symptoms (NYHA I). This group had either persistent left ventricular dilatation and/ or dysfunction yet was better than on presentation.

Patients (or their parents) enrolled in this study have responded to an Informed Consent approved by the local Ethics Committee on Human Research and have found this protocol to be acceptable.

Data Analysis

Continuous data are expressed as median and range or mean ± standard deviation (SD) and categorical data as frequency percentages. Category variable differences were analyzed by chi-square analysis. Differences in continuous variables by Student's paired (bilateral) t test analyses and multivariate correlation tests were used to assess patients' data before grouping. ANOVA test and Student's paired t test were used to assess data after grouping. Probability values ≤ 0.05 were considered significant.

Results

In the current study 51% of patients presented at age one year or younger, and 69 % presented younger than age two, as shown in figure (1).

In the current study of idiopathic DCM, 49 % of patients weighed below the third percentile and 18 % had a positive family history of cardiac disease. Cardiomegaly was noted on chest radiography in 90% of our patients, but only 56.3 % had increased lung vascularity. ST segment and T wave changes were seen on electrocardiogram in 69% of our cases (38 pts). 69% (38 pts) had LVH, 13% (7 pts) had low voltage, and 14.5% had arrhythmias

By comparing echocardiography data for patients on presentation and at last follow-up

using paired T-test, we found a highly significant difference in several areas. These include

inter-ventricular septum dimension in systole, left ventricular systolic dimension, left ventricular posterior wall dimension in systole, end systolic volume, fractional shortening, & ejection fraction, indicating the importance of these indices as valuable indicators for follow-up in this group of patients and as predictors of improvement (shown in table 1)
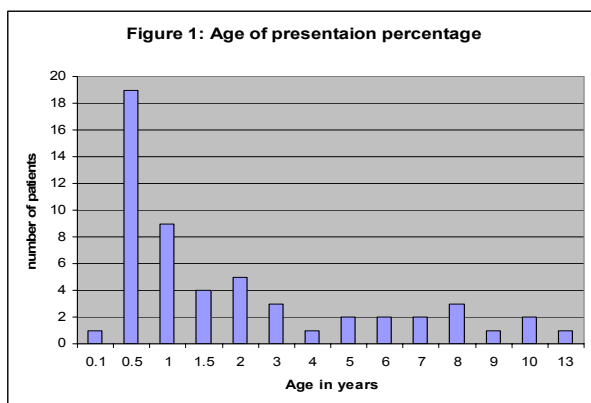

Figure 1: Age of presentaion percentage

Table 1: presents the absolute echocardiography measurements on presentation and follow up

Echo	On presentation	Last follow-up	Significance	
			T-test	P value
IVSd	5.2±1.1 mm	6.7±6.2 mm	-1.89	0.067
IVSs	5.9±1.2mm	8.2±6.2 mm	-2.79	0.007
EDd	44.4± 12.5 mm	43.1±11.8 mm	1.33	0.190
EDs	37.5± 12.6 mm	33.4±12 mm	2.89	0.006
VPd	5.52 ± 1.16 mm	5.4± 1.44mm	0.612	0.543
VPs	6.6±1.5mm	8.97± 6.61mm	-2.57	0.013
EDV	96.4±44.9 ml	88.72± 57.7ml	1.11	0.273
ESV	68.1±35.1ml	53.4± 47.4ml	2.68	0.003
SV	27.7±13.8ml	35.4± 16.7ml	-3.12	0.003
FS	13.8±5.6 %	23.3 ± 9.5%	-7.53	0.000
EF	29.4±9.98 %	47.1± 17.3%	-7.47	0.000

IVSd: Interventricular septum in diastole IVSs: Interventricular septum in systole LVEDd: Left ventricular dimension in diastole LVEDs: Left ventricular dimension in systole LVPd: Left ventricle posterior wall in diastole LVPs: Left ventricle posterior wall in systole ESV: End systolic volume EDV: End diastolic volume SV: Stroke volume FS: Fractional shortening EF: Ejection fraction Data presented as: mean ± standard deviation.

By grouping patients according to outcomes as presented in figure 2: 25 patients (45.5%) improved (group I), 17 patients (30.9%) had a stationary course (group II) and 13 patients (23.6)

(group III) deteriorated, and eventually 11 died (20%). Survival rate over a mean follow-up period of about 3 years (36.2 ± 22.1 months) was 80%.

Prognosis tends to be worse the older the age of first presentation but this tendency did not reach statistical significance (P=0.053) by t-test. However, by ANOVA testing of age in the three groups, the relationship was significant with P value= 0.029 as shown in table 2.
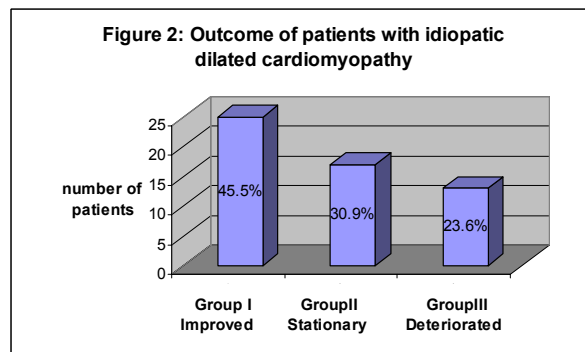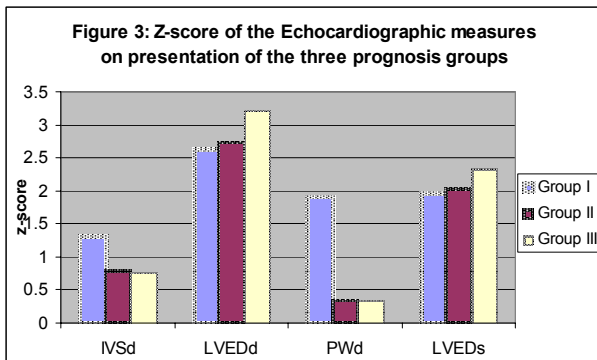

Figure 2: Outcome of patients with idiopatic dilated cardiomyopathy

Table2: The mean age in the three outcome groups and their significance.

	Group I improved	Group II stationary	Group III deteriorated	Significance (ANOVA)	
				F change	P value
Mean age ± SD	26.7± 28.2 months	19.7± 29.9 months	54.2± 52.2 months	3.81	0.029

In the current study, prognosis was correlated significantly with end diastolic volume (P=0.05) as well as the stroke volume (P = 0.04) but not with SF or EF on presentation as measured by all statistical tests.

Since there was a wide range for both the patients' group age & consequently basal surface area (BSA), we calculated the z-score of echocardiographic measures on presentation. Then an inter-groups correlation was performed. This revealed the z-score of interventricular septum dimension in diastole (IVSd) and ventricular posterior wall dimension in diastole (LVPd) were significantly higher in the improved group (group I) when compared to the other groups (group II was stationary & group III deteriorated). There was a p-value 0.01 & 0.007 respectively. Left ventricular end diastolic dimension (LVEDd) was significantly higher in the group that deteriorated (group III) with a P value 0.004, and Left ventricular end systolic dimension (LVEDs) tended to be higher as well, yet did not show a significant difference between groups (p value 0.122) as illustrated in figure (3).

Figure 3: Z-score of the Echocardiographic measures on presentation of the three prognosis groups

Discussion

Dilated cardiomyopathy (DCM) is one of the most common causes of heart failure among children and is often progressive despite maximal medical therapy [17]. DCM constitutes the principal indication for pediatric cardiac transplantation [18]. Although the outcomes of cardiac transplantation among children are improving steadily, there is a paucity of donor organs and an increasing number of patients being listed, as well as persistent concerns regarding intermediate and long-term morbidity and death [17]. The epidemiology and clinical course of DCM in children are not well established and most children have an undiagnosed cause of DCM, which limits the potential for disease-specific therapies [5].

Regarding age of presentation: half of our study group patients presented younger than age one and about 70% presented before their second birthday which is consistent with most published data. In a nationwide Finnish study carried out by Arola, et al, it was found that 52% of IDCM occurs in the first year of life [4]. Also, Towbin, et al, reported a higher incidence in infants (<1 year) than in children (4.40 vs. 0.34 cases per 100 000; P<.001) [5]. Similarly Venugopalan stated that studies suggest 50% of patients with new onset IDCM are younger than age two [12]. Some investigators reported a median age at diagnosis of 13 months which is very close to our patients' median age: 12 months [4]. Similarly, in a Turkish study, they reported median age at diagnosis to be 14 months [12].

Regarding sex of patients: In the USA, the annual incidence is higher in boys than girls (0.66 vs. 0.47 cases per 100 000; P<.001) [5]. In our study, 65.5% of patients were female, whereas in the Finnish study 52% were male, and there was a male preponderance in most published studies as well [7 & 19]. Others have reported no sex predilection exists [12]. These differences may be attributable to racial basis.

Regarding family history: Ten patients (18 %) in our study group had familial cardiomyopathy. Similarly, Michels, et al, in a prospective study demonstrated a prevalence of familial disease in 20% of index cases [20]. Also, other studies have shown that genetic causes account for more than 30% of DCM [21].

The measure of improvement: over time improvement of IVSs, LVEDs, LVPs, ESV, SV, EF & FS has been observed in our patients (before grouping) over the follow-up period. This was not observed regarding left ventricular diastolic dimension. Similarly, other investigators found that the overall time interaction was observed and a significant difference could be seen within the first 6 months after diagnosis in the case of LVEDs and FS, whereas this was not observed when LVEDd was analyzed [4].

Regarding the outcome: of the current study group: about half of our patients improved, which is similar to recently published results which showed 52.5% of patients recovered [12]. In other studies, it has been reported that after a median follow-up period of 2.5 years, about one- third of patients fully recovered, 38% survived with left ventricular dysfunction, and 29.4% died, most in the first year of follow-up [22]. This was similar to our results that most deaths occurred in the first year of follow-up. Similarly, other researchers have stated that 33% of DCM cases improve with signs of improvement seen in the initial six months and continued improvement over two years [23]. However, Arola, et al, reported one-, three-, and five-year survival rates of 65%, 56%, and 51%, respectively [4]. This may be explained by other studies which showed that hospital mortality has been significantly reduced with the use of mechanical assistance and early listing for transplantation [24].

Our total survival rate was 80% with a mean of about 3 years follow up. Similarly, other authors have reported a 16% mortality in DCM children awaiting transplantation [8]. Also Burch, et al, reported 79% survival rates at one year and 61% survival rates at five years [25].

In general, scientists have stated that approximately one third of patients die from the disease, one third of patients continue to have chronic heart failure requiring therapy, and one third of patients experience improvement [12].

Predictors of outcome: In our study group, younger age at presentation was a predictor of favorable outcomes in children with idiopathic dilated cardiomyopathy. This is similar to results obtained by other researchers who stated that good outcome is related to age less than two years at presentation [15]. Also recent reports

stated that older age at diagnosis was a risk factor for subsequent death or transplantation [5]. And Burch, et al, reported that age at presentation greater than two years was a predictor of adverse outcomes [25].

In the current study prognosis was correlated significantly with end diastolic volume as well as the stroke volume & not with SF or EF on presentation by all statistical tests. Similar to our results, some researchers have stated that there were no significant differences between survivor and non-survivor DCM patients regarding echocardiographic left ventricular end diastolic dimension, shortening fraction & left ventricular ejection fraction [26]. However, Towbin, et al, stated that lower left ventricular fractional shortening Z score was risk factor for subsequent death or transplantation [5]. Others have stated that unfavorable prognosis was more frequently associated with lower mean FS [27] which is different from our results but they used Metaiodobenzylguanidine (MIBG) scintigraphy imaging rather than echocardiographic measurements.

The higher z-score result of IVS & LVP in diastole was significantly related to favorable outcomes. Similarly, previous research proved that a relatively thicker posterior wall (with a ratio to the cavity dimension > 0.17) was associated with better prognosis [28]. Also, we found that higher z-score of LVEDd was significantly related to unfavorable outcome which is similar to Arola, who stated that a more favorable outcome was constantly seen in patients with LVEDD 2 SD units [4].

Conclusion

Our results suggested that in children with idiopathic dilated cardiomyopathy: younger age of presentation, higher z-score of inter-ventricular septum and left ventricle posterior wall dimension in diastole are predictors for favorable outcomes, and left ventricular end diastolic dimension of high z-score is related to unfavorable outcomes. It is imperative to develop novel strategies for optimizing new methods for early diagnosis and risk stratification, as well as new therapies for infants and children with dilated cardiomyopathy to avoid transplantation and premature death.

Acknowledgement

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