Cardiol Young 2009; 19: 145–151
© Cambridge University Press
ISSN 1047-9511
doi:10.1017/S1047951109003497
First published online 19 February 2009

Original Article

Clinical profiles and outcomes for Omani children with dilated cardiomyopathy seen in a regional referral hospital

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Abstract *Objective:* To provide an account of paediatric dilated cardiomyopathy as seen in a region of Oman, analysing the data from 32 consecutive children who received care in our unit between January, 1999, and August, 2007. *Results:* The patients, of whom 17 were male, were aged between 5 weeks and 8 years at presentation, with a median of 7 months. The disease was deemed to be myocarditis-induced in one-third, and idiopathic in half. Cardiac failure, seen in almost four-fifths, was the most frequent presenting feature. Correspondingly, the cardiothoracic ratios were increased, to a mean of 68% in 20 infants, and to 65% in 8 older children, and the left ventricular ejection fraction depressed, to a mean of 41%, in the 23 patients in whom it could be evaluated. Patients in cardiac failure received various combinations of diuretics, inotropes, and captopril. In addition, 6 received carvedilol, and 3 intravenous immunoglobulin. Death occurred in 2 patients shortly after admission, one left the hospital against medical advice, and the remaining 29 were followed-up for a mean of 37 months, with a range from 2 to 102 months. Recovery was noted in one-third of the patients, with one-quarter showing improvement but still requiring anti-failure medications. Slightly over two-fifths died. Of those with the idiopathic form, 40% died, with death occurring in 46% of those deemed to have myocarditis-induced disease, in half of those presenting in infancy, and in 57% of those who presented in cardiac failure. *Conclusion:* Dilated cardiomyopathy was often severe in our patients, albeit that the cause was frequently uncertain, and the response to standard anti-failure treatment unsatisfactory. Efforts should be intensified for unravelling its aetiology and improving medical treatment.

Keywords: Heart muscle disease; dilated left heart

Dilated cardiomyopathy describes a myocardial disease, of diverse aetiology, which is characterized by left ventricular dilation and systolic dysfunction.[1] It has been reported from several countries,[2–7] and described for several age groups.[8] Remarkably, most of the reports have drawn attention to the generally severe course of the disease, and especially to its unsatisfactory response to standard anti-failure medication.[2–4,7,9] Reports have mostly come from tertiary centres, raising the possibility of a selection bias in favour of the very sick patients. Reports of the disease in Arab children are scanty.[10,11]

We provide services in paediatric cardiology in a secondary-tier referral hospital that serves a defined region in Oman. Practically all children with known or suspected cardiac disease are referred to us from the general hospitals for evaluation and care. This system of delivery of health care has enabled us to provide for virtually all patients with paediatric cardiac disease in the region, and to build a database. It is the part of the data relating to dilated cardiomyopathy that forms the material for this study, which aimed to provide an account of the disease as seen in a circumscribed region of Oman.

Patients and methods

We commenced our service in Nizwa Hospital in January, 1999, and simultaneously established a

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Accepted for publication 23 November 2008

database. Summaries of patients with cardiac disease were recorded in the database, and the full details in the main files of the hospital. Between January, 1999, and August, 2007 the lone paediatric cardiologist in the department (OJ) evaluated 787 children with various forms of cardiac disease. Of this number, 32 (4%) fulfilled the standard criterions for the diagnosis of dilated cardiomyopathy.[1] They formed the subjects of this study. The evaluation in each patient comprised history and physical examination, chest radiograph, electrocardiograph, and echocardiography. Determination of the levels of the cardiac enzymes creatinine kinase and troponin in the serum was not considered a critical investigation. Blood samples were sent for identification of viruses, but none of them was positive.

In 30 of the 32 patients, the echocardiographic studies at presentation and during follow-up were performed by the same paediatric cardiologist (OJ). The remaining two had initial echocardiography in a neighbouring tertiary hospital, but were subsequently referred to us for continuing care. Follow-up investigations, comprising mostly chest radiographs and echocardiographs, were performed as often as the clinical state warranted.

Statistics

Where necessary, the accrued data were subjected to statistical evaluation, using a GraphPad programme installed in a personal computer. Categorical data were subjected to Fisher's exact test, and continuous data to Student's "t" test. Values less than 0.05 were interpreted to denote statistical significance. We constructed a Kaplan-Meier curve to assess the survival of the patients.

Results

Bio-data

At initial presentation, the patients had been aged between 5 weeks and 8 years, the median age being 7 months and the mean 18.66 months. Of the number, 24 (75%) were less than 12 months old, 5 (16%) were aged between one and 5 years, and only 3 (9%) were more than 5 years old. Both sexes were affected, there being 17 males and 15 females. All the patients were Omani Arabs.

Aetiology

Diagnosis of myocarditis-induced dilated cardiomyopathy was based wholly on clinical findings, specifically the association of acute myocardial failure with a concurrent or recent clinically obvious viral infection in a child who had no other obvious cause for the cardiac disease. Using this criterion, we deemed 11 (34%) of the cases to be myocarditis-induced, and 16 (50%) to be idiopathic. In 2 patients (6%), there was syndromic disease, Noonan's and Pierre-Robin syndromes, but without pulmonary hypertension. In 2 other patients, siblings had reportedly suffered from the same disease, and these patients were categorized as being familial. The remaining patient developed dilated cardiomyopathy after a turbulent neonatal course marked by birth asphyxia and tachyarrhythmias.

Cardiac state at presentation

In 25 (78%) patients, we found evidence of congestive cardiac failure, while 7 (22%) were compensated. Of these 7, 5 had radiographic and echocardiographic features compatible with the disease, while the remaining 2 had been diagnosed and treated earlier in a neighbouring tertiary hospital. The cardiothoracic ratios in these two patients were 44%, and 59%, respectively. In 26 others in whom the ratios could accurately be evaluated, they ranged from 59 to 77, with a mean of 65.7%, and a median of 65%. The ratios in infants and older children are shown in Table 1. They exceeded 60% in 18 (90%) of the 20 infants, and were over 55% in 6 of the 8 older children.

Echocardiographic aspects

Echocardiographic studies in 3 patients comprised only cross-sectional scanning at the time of admission. Of these, 2 died a few hours later, before further studies could be performed, while the third was discharged against medical advice immediately the diagnosis was conveyed to his parents. Further studies were performed in the remaining 29 patients. Of the 2 patients who had received treatment earlier elsewhere, 1 had normal findings, while the other had mild left ventricular dilation with normal contractility. The remaining 27 had left ventricular dilation with varying degrees of impaired contractility. The left ventricular ejection fraction, which was measured in 23 of them, ranged

Table 1. Cardiothoracic ratios in 28 patients.

Cardiothoracic ratio (%)	Infants (n = 20)		Older children (n = 8)	
	No.	%	No.	%
⩽55	–	–	2	25
55–60	2	10	1	12.5
61–65	6	30	3	37.5
66–70	7	35	–	–
>70	5	25	2	25
Median	68		65	
Mean	66.45		62.5	

https://doi.org/10.1017/S1047951109003497 Published online by Cambridge University Press

Table 2. Left ventricular ejection fraction in 23 patients.

Ejection fraction (%)	Percent of patients
25 or less	8.5
26–30	17.5
31–35	8.5
36–40	13.0
41–45	4.5
46–50	30.5
More than 50	17.5

from 21% to 59% (Table 2), with a mean of 40.9% and median of 43%. In 19 (83%) of these, the ejection fraction was 50% or less, far below the level of 64% widely accepted in routine practice as the cut-off between normal and impaired contractility.[12]

Of the 29 patients, 14 (48%) had mitral regurgitation, which was moderate to severe in 10 and mild in four. No patient had intracardiac thrombus or significant pericardial effusion. Left ventricular non-compaction was not recognized in any patient.

Medication

Of the 25 patients who presented in cardiac failure, all received various combinations of standard anti-failure drugs. Later in the course of the disease, 8 patients received infusions of dopamine and dobutamine when they became critically ill. A captopril-induced intolerable cough developed in 4 patients, which necessitated the drug being replaced by lisinopril.

Carvedilol was additionally administered in 6 patients, of whom 3 died. Among the dead was an infant in whom the drug exacerbated the cardiac failure and precipitated severe hepatic and renal failure. The drug was discontinued and the patient survived that crisis, but died later in relentless cardiac failure. In 3 patients, we instituted empirical treatment with L-carnitine, without any benefit. Later in the series, 3 patients with probable acute myocarditis received intravenous immunoglobulin. All responded satisfactorily.

In all, the number of anti-failure medications received by each of the 29 evaluable patients ranged from nil, in those not in failure, to 9, with a mean of 3.4 and a median of 3. The number required by 18 surviving patients, at a mean of 2.3, was significantly lower than the mean of 5.1 required by the 11 patients who subsequently died (t equal 4.02, p equal 0.0004, and 95% confidence interval equal to -4.17 to -1.35).

Follow-up and outcome

Of our overall group, 2 patients died shortly after admission, and another was taken away the day the diagnosis was made. The remaining 29 patients were followed for periods ranging from 2 weeks to 102 months, with a mean of 36.88 and a median of 21 months. We followed 9 (31%) for less than 12 months, 13 (45%) for from 1 to 5 years, and 7 (24%) for more than 5 years. The cumulative duration for all the 29 patients was 95.24 patient-years.

The outcome is uncertain in two of the 32 patients, these being the patient who was taken away from hospital, and another who defaulted from hospital after follow-up of 5-years. Of the remaining 30 patients, 10 (33%) have made a clinical recovery and are not on any cardiac medications. An additional 7 patients (24%) are alive and are improved, but still need anti-failure medications. The remaining 13 patients (43%) have died, 7 (54%) within 12 months of the first presentation, and 4 others (31%) within 24 months. The remaining 2 deaths occurred after 30 and 60 months of follow-up, respectively. Mortality in the first half of the study, from 1999 through 2003, was 33%, but during the second half it rose to 53%, with 8 of 15 patients dying. These rates are not statistically significant (p equal to 0.46). The Kaplan-Meier curve (Fig. 1) demonstrates the dismal outlook for the patients, with the probability of survival down to about 50% at 72 months after presentation.

Of the 13 deaths, 11 occurred in hospital, 10 from treatment-resistant cardiac failure, and one from a combination of failure and severe varicella pneumonia. The remaining 2 deaths occurred suddenly at home. The cause of death was uncertain, but cardiac arrhythmia was suspected.

Predictors of adverse outcome

The data relating to age, sex, aetiology and the cardiac state at presentation, were analysed in relation to the outcome with a view to determine if they had any predictive value (Table 3). The effect of age was assessed in all 30 patients whose entire course was known to us. This cohort included 22 infants, 11 (50%) of whom have died. Of the five children aged between 1 and 5 years, 1 has died; and so also has 1 of the 3 patients aged more than 5 years.

The rates of death were comparable for males (40%) and females (47%). A similar picture emerged in respect of the aetiology. The mortality was high in idiopathic cases (40%), as well as in those with probable myocarditis (46%). Of the 2 patients with syndromic disease, 1 has died, as has the only patient with familial disease who received long-term care in our hospital.

Of the 30 patients under consideration, 23 (77%) presented in cardiac failure, with 13 (57%) of these subsequently dying. In contrast, all 7 patients who were not in failure have survived to date. The difference in rates of death is significant (p equal 0.01).

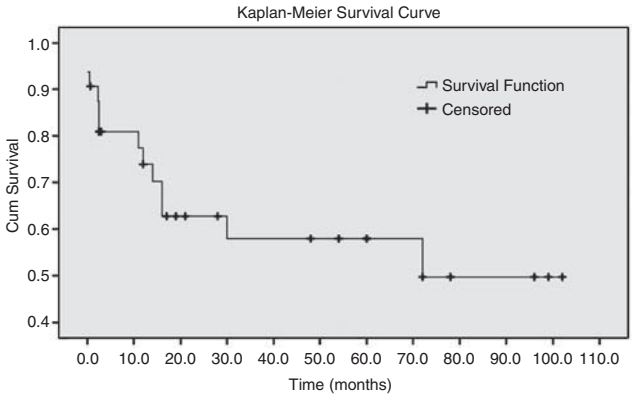

Figure 1.
Kaplan-Meier survival curve for our 32 Omani children with dilated cardiomyopathy. Note the high mortality, especially in the first 2 years of follow-up.

Table 3. Mortality matched against selected parameters.

Parameter	No. of patients	Died	Mortality rate (%)	'p'
Age (n = 30)				
0–12 mo	22	11	50	Not significant
1–5 yr	5	1	20	
>5 yr	3	1	33.3	
Sex (n = 30)				
Male	15	6	40	Not significant
Female	15	7	47	
Aetiology (n = 29)				
Idiopathic	15	6	40	Not significant
Myocarditis	11	5	46	
Syndromic	2	1	50	
Familial	1	1	100	
Heart failure at presentation (n = 30)				
Absent	7	Nil	Nil	0.01
Present	23	13	56.5	
Left ventricular EF (n = 23)				
Below 50%	19	8	42	Not significant
⩾50%	4	1*	25	

EF: Ejection fraction.
*: Death due in part to varicella pneumonia.

The cardiothoracic ratios at presentation were calculated in 28 patients, one of whom was later taken away. Of the remaining 27, 17 are alive, while 10 have died. The ratios in those who did not survive, at 44% to 77%, with a mean of 70.3%, were significantly higher than the values in the surviving patients, which ranged from 62% to 77%, with a mean of 62.1% (t equal 3.19, p equals 0.004, and 95% confidence intervals equal 2.90 to 13.46).

At presentation, the left ventricular ejection fraction was measured echocardiographically in 23 patients, 9 of whom have since died. It was less than 50% in 8 of these 9, and was 54% in the ninth patient, who succumbed to a combination of cardiac failure and varicella pneumonia. The fraction was also low in the 14 surviving patients, exceeding 50% in only 3 (21%) of them. The mean was slightly higher in surviving patients, at 42.1%, than in non-survivors, where the value was 38.9%, but the difference was not statistically significant (p equal 0.52).

Discussion

Our account of dilated cardiomyopathy based on experience in a regional referral hospital in Oman corroborates the dismal accounts of the disease

https://doi.org/10.1017/S1047951109003497 Published online by Cambridge University Press

Table 4. Summary of outcomes in some publications on childhood dilated cardiomyopathy.

Lead author	Year	Country	Aetiology	No. of patients	Death or transplant (%)*
Griffin[2]	1988	USA	Mixed	32	53
Akagi[3]	1991	Canada	Mixed	25**	80
Burch[4]	1994	UK	Idiopathic	63	39
Ciszewski[13]	1994	Poland	Mixed	19	37
Arola[9]	1998	Finland	Idiopathic	62	56
Nogueira[14]	2000	Portugal	Idiopathic	34	29
Seliem[11]	2000	Saudi Arabia	Familial	55	46
Venugopalan[15]	2001	UK	Mixed	39	31
Azevedo[16]	2004	Brazil	Idiopathic	142	25
Gagliardi[6]	2004	Italy	Mixed	114	35
Tsirka[17]	2004	USA	Mixed	91	34
Weng[7]	2005	Taiwan	Idiopathic	18	72
Daubeney[18]	2006	Australia	Mixed	184	37
Towbin[19]	2006	Canada/USA	Mixed	1426	46
Present study		Oman	Mixed	32	43

Mixed: Indicates mixture of idiopathic and myocarditis – induced cases.
*: Where actuarial figures are given survival at the longest follow-up was selected for this table.
**: All patients older than two years.

which have been published previously from other countries (Table 4). During a mean follow-up period of 37 months, slightly more than two-fifths of the patients died, approximately one-fifth improved but continued to require anti-failure medications, and only a third recovered, apparently fully. These figures raise the very important question on why the standard medical treatment of the disease is so frequently unsatisfactory.

In all likelihood, the extent of myocardial disease is the major factor, modified, perhaps, by other cause-specific factors. And since the causes are numerous[8,19] so also will be the factors that could influence the outcome. Previous publications suggest that, in general, patients with severe cardiac failure at presentation fare poorly[14,16,19,20] while the prognosis appears to be better in cases induced by myocarditis.[5,6,19] The influence of age is unclear. A better outcome in children aged below 2 years has been reported by several authors,[2,4,9,19,20] but countered by others.[15,16,17,21,22] In our series, the mortality was high in patients who presented in heart failure, in infants, and in those with both idiopathic and myocarditis-induced disease. Thus, factors that influence the outcome still need further clarification.

A limitation in our study relates to the diagnosis of infective myocarditis which, for technical reasons, was wholly clinical. Strictly, there are no flawless criterions for the clinical diagnosis of myocarditis. Elevation of cardiac enzymes is an unreliable criterion, because the levels are rarely raised, and the sensitivity of testing is as low as 33 percent.[23] Indeed, the recent statement from the American Heart Association on cardiomyopathies[8] does not recommend the test for the diagnosis of myocarditis. Endomyocardial biopsy, evaluated using the Dallas criterions,[24] remains the gold standard for diagnosis. But even that test is not fail-proof. Endomyocardial biopsy is not feasible in most centres that provide care for children with cardiac disease. Even when feasible, the biopsy taken may miss areas of inflammation, and hence provide false negative results.[8,25] The clinical implication of all these factors is that in many centres, including ours, the aetiology of dilated cardiomyopathy is often uncertain.

Our experience uncovers an epidemiological aspect of the disease that appears relevant to its aetiology. Of those aged under 5, we saw 3.37 cases per year, for a population of 34,186, which translates into an annualized incidence of 9.86 cases per 100,000 children. This figure is much higher than the reported incidence of 1.13 per 100,000 infants and children in the United States of America,[19] 3.8 per 100,000 Finnish infants,[9] and 4.8 per 100,000 in Australian infants.[20] The higher incidence in our region probably reflects a high incidence of infection, and may be a subtle evidence that myocarditis is a major aetiological factor in our patients, albeit not identified with certainty.

In the absence of a clearly identified aetiology, treatment aimed at the cause is either impossible or, at best, empirical. This has been a particular concern in cases suspected to be induced by myocarditis, where immune-modulation therapy seems to be effective.[6] We formulated that diagnosis on clinical grounds in one-third of our patients, and hesitantly administered intravenous immunoglobulin to 3 patients who presented later in the series.

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Interestingly, all 3 have survived to date. But, since they are few, there is a need for caution in crediting their survival to immune-modulation therapy. Besides, although the evidence for the efficacy of immune modulation therapy is strong for those known to have myocarditis-induced disease,[6] it is not incontrovertible.[26] Consequently, other therapeutic options are being explored, among them the use of growth hormone to reinvigorate the myocardium.[27,28] Here, too, the initial reports are encouraging, but it remains to be seen if that option will evolve into an effective and widely applicable remedy.

Currently, cardiac transplantation is the ultimate surgical resort for patients who do not respond satisfactorily to medical treatment. But that option is available only in relatively few centres, most of them in Europe and the United States of America. For the paediatrician who has no recourse to cardiac transplantation, caring for a child with dilated cardiomyopathy and treatment-resistant cardiac failure remains a very challenging assignment. Quite often, the choice must be made between continuing treatment with barely effective conventional drugs, adding carvedilol despite its ill-defined paediatric dosing and lingering uncertainties about its efficacy in children,[29,30] or administering intravenous immunoglobulin without histological confirmation of myocarditis. In all probability, the choice will be influenced as much by the available resources as by the embraced philosophies of care.

In conclusion, dilated cardiomyopathy is often severe in our patients. While the clinical diagnosis is usually easy, and the haemodynamic severity can be ascertained fairly accurately, the atiology is frequently uncertain. That renders cause-targeted treatment impossible, or at best empirical. The response to standard anti-failure medical treatment is often unsatisfactory; and cardiac transplantation is not feasible. For now, therefore, hopes of improved survival in ours, and similar centres, are hinged on on-going international efforts to manipulate the immune mechanisms implicated in myocarditis-induced cases, or generally to reinvigorate the myocardium through treatment with growth hormone.

Acknowledgment

We thank the paediatric residents who provided care for the patients, Dr Rizwi of Sultan Qaboos University for assistance with statistical analysis, and Dr Vijay Baichoo, of Corniche Hospital in Abu Dhabi, for useful advice during the preparation of this script. Nizwa hospital authorities provided much needed administrative support.

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