

## Original Research Article

# Clinical course and prognosis of dilated cardiomyopathy in children

Iranna S. Hirapur<sup>1</sup>, Ravindran Rajendran<sup>2\*</sup>, Jayaranganath<sup>3</sup>, Manjunath Nanjappa<sup>3</sup>

<sup>1</sup>Department of Cardiology, Mahadevappa Rampure Medical College, Kalaburagi, Karnataka, India

<sup>2</sup>Department of Cardiology, Trichy SRM Medical College Hospital and Research Centre, Irungalur, Tamilnadu, India

<sup>3</sup>Department of Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research centre, Bangalore, Karnataka, India

**Received:** 30 August 2019

**Revised:** 03 September 2019

**Accepted:** 27 September 2019

### \*Correspondence:

Dr. Ravindran Rajendran,

E-mail: [rravindranrajendran@gmail.com](mailto:rravindranrajendran@gmail.com)

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ABSTRACT

**Background:** Epidemiology and clinical course of dilated cardiomyopathy (DCM) in children and infants are not well established. Thus, this study aims to investigate the clinical course and prognosis of DCM in children

**Methods:** This was a single-center, prospective, observational study conducted at a tertiary-care center in India between February 2011 and September 2012. A total of 31 patients admitted to the paediatric department diagnosed with DCM were included in the study. Patients were divided into three groups based on the age at the time of diagnosis: 0-3 years, >3-12 years and >12-16 years. Among the study population, 28 patients were followed up for a mean period of 1.44 years and three patients were lost to follow-up.

**Results:** Of the 31 patients, 11 patients were male with a mean age of  $8.9 \pm 6$  years and 20 patients were female with a mean age of  $8.3 \pm 6$  years. All patients were presented with same characteristics of New York heart association (NYHA) class III-IV dyspnoea and fatigue. Among 28 patients who were followed-up for a mean period of 1.44 years, 20(71.4%) patients died and eight patients were on follow up. Of the eight patients, five patients were with NYHA class III symptoms and three patients were with NYHA class I-II symptoms.

**Conclusions:** Dilated cardiomyopathy in children is a very serious disease with a grave prognosis. Patients with NYHA III-IV symptoms have a very high mortality rate and potential use of other therapies remains to be fully evaluated in paediatric population.

**Keywords:** Children, Dilated cardiomyopathy, Dyspnoea, Fatigue, Myocarditis, Prognosis

### INTRODUCTION

Cardiomyopathies are a heterogeneous group of myocardial diseases with multifactorial etiologies that affect ventricular systolic function, diastolic function or both. Cardiomyopathies are classified by the World Health Organization (WHO) as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy, restrictive cardiomyopathy and arrhythmogenic right ventricular dysplasia-cardiomyopathy.<sup>1</sup>

However, numerous cardiomyopathies should still be classified as idiopathic.<sup>2</sup> DCM is the most common form of cardiomyopathy characterized by a dilated left ventricular (LV) chamber and systolic dysfunction that commonly results in congestive heart failure.<sup>3,4</sup> Although cardiomyopathies have multifactorial etiology in both children and adults, genetic defects play a more important role in infants and children.<sup>5</sup> The underlying causes in adults are usually coronary artery disease (CAD)<sup>4</sup>, inflammatory heart disease, myocardial toxins and

genetic defects.<sup>3,6</sup> Around 30-35% of patients are reported to have a genetic form of DCM.

Dilated cardiomyopathy is the leading cause of cardiac transplantation in children.<sup>3</sup> Cardiac transplantation as a form of treatment is yet to be practical in India. The decision to proceed with cardiac transplantation for paediatric DCM is complicated by the possibility that these patients can demonstrate eventual improvement and resolution for LV dilation and dysfunction.<sup>7</sup> Besides cardiac transplantation, other new therapies such as metabolic component supplementation, angiotensin-converting enzyme (ACE) inhibition and most recently beta-blockade have been utilized as therapy that may also affect outcome or improvement in LV structure and function.<sup>8-10</sup> The incidence of DCM in infants and children in USA, UK and Australia is between 0.34 and 1.13 per 1, 00,000 per population.<sup>11,12</sup> There are very few studies that have been done in India and numerous recent studies carried out in children have focussed on the diagnosis of cardiomyopathies, but only a few reports have been published on their epidemiology during the era of modern diagnostic methods.<sup>2,13,14</sup> Hence, the epidemiology and clinical course of DCM in children and infants are not well established. Thus, this study was conducted to investigate the clinical course and prognosis of DCM in paediatric patients.

## METHODS

### *Study design and patient population*

This was a single-center, prospective, observational study conducted at a tertiary-care center in India between February 2011 and September 2012. A total of 31 patients admitted to the paediatric department diagnosed with dilated cardiomyopathy were included in the study. Patients were divided into three groups based on the age at the time of diagnosis: 0-3 years, >3-12 years and >12-16 years. Children with new onset of acute heart failure symptoms and whose parents/guardians gave informed consent were included in the study. Patients with congenital heart defects, valvular heart disease, rheumatic heart disease, chronic arrhythmia and restrictive or hypertrophic cardiomyopathy were excluded from the study.

### *Study procedure*

Detailed work-up for an etiological diagnosis was not possible in all cases because of financial and ethical concerns, but an effort was made to classify possible etiology based on the available data from history, physical findings and basic investigations. Patients who had a history of fever in the preceding three months were considered to have possible myocarditis as the cause of dilated cardiomyopathy. All patients underwent routine blood investigations such as hemoglobin, total cholesterol, differential count (DC), erythrocyte sedimentation rate (ESR), renal function tests (RFT),

serum electrolytes (SE), liver function tests (LFT), calcium (Ca<sup>2+</sup>), magnesium (Mg<sup>2+</sup>), thyroid function tests (TFT), human immunodeficiency virus test (HIV), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), venereal disease research laboratory test (VDRL), and blood Grouping with Rh typing. Electrocardiography (ECG), chest x-ray and echocardiography were done at baseline and repeated as indicated by the clinical scenario. Coronary angiogram was done in two children to rule out anomalous left coronary artery from the pulmonary artery (ALCAPA). Patients were treated with Inj. dobutamine at a dose of 5-10 mcg/kg/min intravenously (gradually titrate upward to the desired effect for 24 hrs) for inotropic support and Inj. Lasix at a dose of 1mg/kg/dose intravenously (t.i.d. to q.i.d.). Once the initial failure symptoms started to improve, beta-blockers, ACE inhibitors and digoxin were used in the recommended dosage wherever appropriate. Patients with LV clot received anticoagulation with acitrom to the INR of 1.5-2.

### *Data collection*

Age, gender, symptoms, duration of onset of symptoms, blood pressure, heart rate, height and weight were noted for all the patients at the time of admission. Patients presenting with cardiomegaly are often associated with congestive heart failure (CHF) and evidence of an unobstructed, dilated, poorly contracting LV were identified and labelled as having dilated cardiomyopathy. The in-hospital outcome and subsequent course after successful discharge were noted.

### *Follow-up*

After discharge, all patients were followed up at three monthly intervals through the outpatient department (OPD) basis or telephonic contact. Twenty-eight patients were followed up for a mean period of 1.44 years and three patients were lost to follow-up. The three patients who were lost to follow-up were below three years of age.

### *Statistical analysis*

Continuous variables were represented as mean  $\pm$  standard deviation and as minimum-maximum wherever appropriate. Categorical variables were represented as numbers and percentages. The Student's t-test or Mann-Whitney U test was used to compare continuous variables and Chi-square test was used to compare categorical variables. The analysis of variance (ANOVA) and Kruskal- Wallis test was used wherever appropriate. The correlation between certain variables of the treatment groups was performed using the Spearman correlation analysis. A p-value of <0.05 was considered to be statistically significant. All statistical analyses were performed using the statistical package for the social sciences (SPSS) 16.0 version (SPSS; Chicago, Illinois, USA).

## RESULTS

### Baseline characteristics

A total of 31 patients diagnosed with DCM were included in the study. Of the 31 patients, 11 patients were male with a mean age of  $8.9 \pm 6$  years and 20 patients were female with a mean age of  $8.3 \pm 6$  years. Patients were divided into three groups based on the age at the time of diagnosis: 0-3 years, >3-12 years and >12-16 years. Ten, eight and 13 patients were included in 0-3 years, >3-12 years and >12-16 years group, respectively. All patients were presented with the same characteristics of New York heart association (NYHA) class III-IV dyspnoea and fatigue. The baseline characteristics of the study population were displayed in Table 1.

### Etiology

Among the study population, seven patients had history suggestive of fever in the preceding three months suggestive of possible myocarditis, one patient was HIV positive, one patient was diagnosed with diphtheric myocarditis and died within 15 days of diagnosis and one patient had chronic kidney disease (CKD) and is waiting for renal transplantation. Other blood investigations such as hemoglobin, sodium, potassium, calcium, and magnesium were within the normal range. Merely two patients had borderline thyroid stimulating hormone (TSH) elevation and 22 patients who were diagnosed with dilated cardiomyopathy did not have an explainable cause. The blood investigations of all the patients are outlined in Table 2.

**Table 1: Baseline characteristics of the study population.**

Characteristics	0-3 years (n=10)	>3-12 years (n=8)	>12-16 years (n=13)
Male, n (%)	4 (40%)	2 (25%)	5 (38.5%)
Female, n (%)	6 (60%)	6 (75%)	8 (61.5%)
Dyspnoea, n (%)	10 (100%)	8 (100%)	13 (100%)
Fatigue, n (%)	10 (100%)	8 (100%)	13 (100%)
Fever within 3 months, n (%)	2 (20%)	2 (25%)	3 (23%)

**Table 2: Characteristic comparison of survivors vs. non-survivors.**

Characteristics	Survivors (n=8)	Non-survivors (n=20)	p value
Male, n (%)	3 (37.5%)	8 (40%)	0.903
Female, n (%)	5 (62.5%)	12 (60%)	
Age (mean, years)	96.3	117.3	0.465
Mean EF (mean, %)	25.5	27.1	0.5
BP systolic (mean, mmHg)	86.3	85.5	0.924
BP diastolic (mean, mmHg)	65.7	62.0	0.523
Weight (mean, kg)	23.7	27.0	0.487
Height (mean, cm)	109	122.5	0.361
PASP (mean, mm/hr)	41.6	43.6	0.685
ESR (mean, mg/dL)	10.8	10.8	1.00
Blood urea (mean, mg/dL)	60.9	64.6	0.878
Creatinine (mean, mg/dL)	1.4	1.1	0.659
Sodium (mean, mEq/L)	115	129	0.176
Potassium (mean, mmol/L)	4.1	3.7	0.217
Calcium (mean, mg/dL)	8.6	8.5	0.604
Magnesium (mean, mEq/L)	1.9	1.9	0.943
RBS (mean, mg/dl)	83	101	0.375

EF - Ejection fraction; BP - Blood pressure; PASP - Pulmonary artery systolic pressure; ESR - Erythrocyte sedimentation rate; RBS - Random blood sugar

### Outcomes and its predictors

Of the study population, mild, moderate and severe mitral regurgitation was observed in eight, 15 and five patients, respectively. Fifteen, eight and five patients had mild, moderate and severe tricuspid regurgitation, respectively.

Nine patients had left ventricular clot, five patients had mild pericardial effusion and one patient had moderate pericardial effusion. Two patients had peripheral thromboembolism with one requiring amputation of the left lower limb. There was no statistical difference among various parameters when compared between the survivors

and non-survivors' groups. Fourteen patients had A+ blood group which is statistically significant as compared with the survivor's group ( $p=0.17$ ). Characteristic comparison of survivor's and non-survivors are shown in Table 2. Among 28 patients who were followed-up for a period of 1.44 years, 20 (71.4%) patients died and eight patients were on follow up. Of the eight patients, five patients had NYHA class III symptoms and three patients had NYHA class I-II symptoms.

## DISCUSSION

In this study, clinical course and prognosis of dilated cardiomyopathy in children were analyzed. In this study, majority (42%) of the patients involved were between 12 and 16 years of age at presentation which can be comparable to a study conducted by Tsrika, et al, showing that 25 (27%) patients were over 12 years of age at presentation.<sup>15</sup> In this study, females were found to be a poor predictor of outcome. However, young adult women with idiopathic DCM have been reported to have poor outcomes.<sup>16</sup> Further studies are needed to confirm this finding and investigate potential immunologic or hormonal factors that may contribute to this phenomenon.

The results of the study showed that DCM patient presented with NYHA class III-IV symptoms require urgent admission because they have rapid downhill course. Paediatric DCM may have any of several outcomes and reported 5-year survival rates range between 50% and 60%.<sup>2,17</sup> Although most of the paediatric DCM cases were idiopathic, diagnostic algorithms have increased the proportion of paediatric DCM cases with a known cause.<sup>18</sup> It has been generally reported in studies that a third of patients with DCM die, another third improves and that the remaining third remain stable.<sup>19</sup> As in this study, 71.5% of patients died in the follow-up period of 1.44 years and three patients were lost to follow up. This was in contrast to previous studies because such high mortality has not been shown in any of the published studies.<sup>3,15</sup> The reason could be that all the patients who were admitted to the paediatric department were very sick with NYHA class III-IV symptoms. The outpatient echocardiography data during the same period showed that 78 patients were diagnosed with DCM, these patients were less symptomatic and were managed on OPD basis. Detailed work up and follow up was not possible in these cases.

Paediatric DCM is a diverse disorder with outcomes that depend on the cause, age at presentation and heart failure status. Understanding the cause of DCM has remained difficult as the spectrum of disease aetiologies in childhood has been quite different than that reported in adults. In pure DCM, myocarditis and neuromuscular disorders have been the most common causes during childhood with familial DCM, inborn errors of metabolism, and malformation syndromes have been less common.<sup>3</sup> In adults, coronary artery disease has been a common cause of DCM, which has been rare in

childhood, and explained some differences between incidence rates in childhood vs. adulthood.<sup>3</sup> Medical management has been the only possible treatment in Indian poor children; cardiac transplantation was beyond reach for our patients.

Studies report that major clinical events occurred within one year of presentation.<sup>2,17,20</sup> Additional medical therapies can be used in DCM, which may have contributed to an improved outcome. Preliminary evidence indicates that beta-blocker therapy can improve LV dysfunction in paediatric DCM.<sup>21</sup> The use of ACE inhibitors has been reported to be associated with improvement of LV dysfunction in children.<sup>9</sup> However, administration of ACE inhibitors in larger adult studies, have no indicated improvement, but inhibition of progression of LV dysfunction and dilation with ACE inhibitor administration which was similar to this study. It has been known that medical therapies have not shown to affect outcomes drastically.<sup>3</sup> New diagnostic methods for early detection, risk stratification and new therapies need to be developed for infants and children with DCM to avoid cardiac transplantation and premature death.<sup>15,22,23</sup> Hence more studies on etiology of the disease are needed, genetic counselling should be improved, regional characteristics and familial inheritance should be studied.

This study does have a few limitations. Firstly, the detailed diagnostic tests for myocarditis such as viral serology, endomyocardial biopsy and autopsy were not conducted. Secondly, a small number of patients were enrolled in the study. Thirdly, admitted patients were with higher NYHA class symptoms which accounts for very high mortality. Fourthly, since most of our patients were not well educated and were not financially well off, they were unable to attend the follow-ups regularly.

## CONCLUSION

Dilated cardiomyopathy in children is a very serious disease with a grave prognosis. Patients with NYHA III-IV symptoms have a very high mortality rate. A marked difference in the occurrence of new cases of DCM between infants and older children suggests that different pathophysiologic mechanisms and possible etiologies are involved in the different age groups. The potential for routine use of ACE inhibitors and beta-blockade therapies remains to be fully evaluated in the paediatric population.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

## REFERENCES

1. Richadson P. Report of the 1995 World Health Organization/International Society and Federation of Cardiology. Task force on the definition and



- classification of cardiomyopathies. *Circulation.* 1996;93:841-2.
2. Arola A, Jokinen E, Ruuskanen O, Saraste M, Pesonen E, Kuusela A-L, et al. Epidemiology of idiopathic cardiomyopathies in children and adolescents: a nationwide study in Finland. *Am J Epidemiol.* 1997;146:385-93.
  3. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA.* 2006;296:1867-76.
  4. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association scientific statement from the council on clinical cardiology, heart failure and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention. *Circulation.* 2006;113(14):1807-16.
  5. Ferencz C, Neill CA. Cardiomyopathy in infancy: observations in an epidemiologic study. *Pediatr Cardiol.* 1992;13(2):65-71.
  6. Shaddy RE. Cardiomyopathies in adolescents: dilated, hypertrophic, and restrictive. *Adolescent Med Clin.* 2001;12(1):35.
  7. Lewis AB. Late recovery of ventricular function in children with idiopathic dilated cardiomyopathy. *Am Heart J.* 1999;138:334-8.
  8. Helton E, Darragh R, Francis P, Fricker FJ, Jue K, Koch G, et al. Metabolic Aspects of Myocardial Disease and a Role for L-Carnitine in the Treatment of Childhood Cardiomyopathy. *Pediatrics.* 2000;105:1260-70.
  9. Stern H, Weil J, Genz T, Vogt W, Bühlmeier K. Captopril in children with dilated cardiomyopathy: acute and long-term effects in a prospective study of hemodynamic and hormonal effects. *Pediatr Cardiol.* 1990;11:22-8.
  10. Bruns LA, Canter CE. Should  $\beta$ -blockers be used for the treatment of pediatric patients with chronic heart failure? *Pediatr Drugs.* 2002;4(12):771-8.
  11. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. *N Engl J Med.* 2003;348(17):1647-55.
  12. Nugent AW, Daubeney PE, Chondros P, Carlin JB, Cheung M, Wilkinson LC, et al. The epidemiology of childhood cardiomyopathy in Australia. *N Engl J Med.* 2003;348(17):1639-46.
  13. Kothari S, Dhopeswarkar R, Saxena A, Juneja R. Dilated cardiomyopathy in Indian children. *Indian Heart J.* 2003;55(2):147-51.
  14. Khalil A, Chawla K, Chakravarti A. Dilated cardiomyopathy: clinical profile and treatment. *Indian Pediatr.* 2000;37:1242-6.
  15. Tsirka AE, Trinkaus K, Chen S-C, Lipshultz SE, Towbin JA, Colan SD, et al. Improved outcomes of pediatric dilated cardiomyopathy with utilization of heart transplantation. *J Am Coll Cardiol.* 2004;44:391-7.
  16. McDonagh T, Cunningham A, Morrison C, McMurray J, Ford I, Morton J, et al. Left ventricular dysfunction, natriuretic peptides, and mortality in an urban population. *Heart.* 2001;86:21-6.
  17. Akagi T, Benson LN, Lightfoot NE, Chin K, Wilson G, Freedom RM. Natural history of dilated cardiomyopathy in children. *Am Heart J.* 1991;121:1502-6.
  18. Schwartz ML, Cox GF, Lin AE, Korson MS, Perez-Atayde A, Lacro RV, et al. Clinical approach to genetic cardiomyopathy in children. *Circulation.* 1996;94:2021-38.
  19. BILGIÇ A, ÖZBARLAS N, ÖZKUTLU S, ÖZER S, ÖZME S. Cardiomyopathies in Children Clinical, Epidemiological and Prognostic Evaluation. *Japanese Heart J.* 1990;31:789-97.
  20. Lewis AB, Chabot M. Outcome of infants and children with dilated cardiomyopathy. *Am J Cardiol.* 1991;68(4):365-9.
  21. McNamara DM, Holubkov R, Starling RC, Dec GW, Loh E, Torre-Amione G, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation.* 2001;103:2254-9.
  22. McMahon C, Nagueh S, Eapen R, Dreyer W, Finkelshtyn I, Cao X, et al. Echocardiographic predictors of adverse clinical events in children with dilated cardiomyopathy: a prospective clinical study. *Heart.* 2004;90:908-15.
  23. Rosenthal D, Chrisant MR, Edens E, Mahony L, Canter C, Colan S, et al. International Society for Heart and Lung Transplantation: practice guidelines for management of heart failure in children. *J Heart Lung Transplant.* 2004;23(9):1313-33.

**Cite this article as:** Hirapur IS, Rajendran R, Jayaranganath, Nanjappa M. Clinical Course and Prognosis of Dilated Cardiomyopathy in Children. *Int J Res Med Sci* 2019;7:4218-22.