

REGULAR ARTICLE

The highest mortality rates in childhood dilated cardiomyopathy occur during the first year after diagnosis

Shalan Fadl (shalan.fadl@regionorebrolan.se)¹, Håkan Wåhlander², Katja Fall³, Yang Cao^{3,4}, Jan Sunnegårdh²

1. Department of Paediatrics, Örebro University Hospital, Örebro, Sweden

2. The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Institution of Clinical Sciences, Gothenburg University, Gothenburg, Sweden

3. Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro, Sweden

4. Unit of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

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Correspondence

Shalan Fadl, MD, Department of Paediatrics, Örebro University Hospital, 70185 Örebro, Sweden.

Tel: +46 196021718 |

Fax: +46 19187915 |

Email: shalan.fadl@regionorebrolan.se

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ABSTRACT

Aim: The aim of the study was to assess the incidence, mortality and morbidity of dilated cardiomyopathy (DCM) and noncompaction of the left ventricle (LVNC) in Swedish children.

Methods: We reviewed hospital records of all children with dilated cardiomyopathy (DCM) or left ventricular noncompaction cardiomyopathy (LVNC) up to the age of 18 in the healthcare region of western Sweden from 1991 to 2015.

Results: In total, 69 cases (61% males) were identified. The combined incidence of DCM and LVNC was 0.77 (95% CI 0.59-0.96) per 100 000 person years. Children were divided into six groups, and their outcomes were analysed depending on their aetiology. Idiopathic DCM was reported in 43%, and familial dilated and left ventricular noncompaction aetiology was present in 32%. DCM due to various diseases occurred in 8%. DCM associated with neuromuscular diseases was present in 16%. The overall risk of death or receiving transplants in children with idiopathic and familial DCM was 30% over the study period, and 21% died in the first year after diagnosis.

Conclusion: The combined incidence of DCM and LVNC was similar to previous reports. Most children with idiopathic DCM presented during infancy, and mortality was highest during the first year after diagnosis.

INTRODUCTION

The aetiology and distribution of dilated and noncompaction cardiomyopathy are largely unknown (1). Dilated cardiomyopathy (DCM) is characterised by dilatation and impaired contractility of the left or both ventricles, and the usual presentation is heart failure (2,3). DCM has been associated with significant morbidity and mortality and has been reported to account for more than half of all cardiac transplants in children and adolescents (4-8). Left ventricular noncompaction cardiomyopathy (LVNC) is still referred to as an unclassified cardiomyopathy that may develop into dilated cardiomyopathy—the LVNC-dilated phenotype (9-12). Because LVNCs have several morphological and functional phenotypes, they are difficult to diagnose (10,12). For example, both the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases and the World Health Organization (WHO)

define LVNC as an unclassified cardiomyopathy, whereas the American Heart Association defines LVNC as a primary genetically determined cardiomyopathy, which reflects the embryonic structure of the human heart due to an arrest in the compaction process during the first trimester. Previous studies have reported incidences of DCM between 0.57 and 0.73 per 100 000 person years among children aged between birth and 18 (2,6,13). The occurrence of DCM and LVNC during childhood has not previously been

Abbreviations

DCM, Dilated cardiomyopathy; ICU, Intensive care unit; IDCM, Idiopathic dilated cardiomyopathy; LVEDD, Left ventricular end-diastolic diameter; LVNC, Left ventricular noncompaction cardiomyopathy.

Key notes

- This was the first study to show the distribution and outcomes of childhood dilated and noncompaction cardiomyopathy (DCM) in Sweden.
- We identified 69 cases from 1991 to 2015, and the incidence was 0.77 per 100 000 person years, which was comparable to other western countries.
- The overall risk of mortality or receiving transplants in children with idiopathic and familial DCM was 30%, and the highest mortality was during the first year after diagnosis.

described in Sweden, and we therefore wanted to assess rates and outcomes for these two uncommon conditions.

METHODS AND MATERIALS

Study design

This cohort study was based at the Queen Silvia Children's Hospital in the Western Health Care Region in Sweden. Using the hospital's medical records database, we identified all children up to 18 years of age with DCM or LVNC or patients with familial DCM who had received care at the hospital between January 1991 and October 2015. Individual medical records were reviewed to verify children diagnosed with DCM or LVNC according to the Swedish version of International Classification of Diseases Codes, Tenth Revision (ICD-10)–I42.0, I42.7, I42.8, I42.9–or Ninth Revision (ICD-9) 2.5E. The hospital serves about 2.5 million individuals living in the Western Health Care Region in Sweden, and no private healthcare for these conditions was available at the time.

Materials

All medical records were meticulously reviewed with regard to medical history, family history of cardiac disease, physical examinations and the results of all investigations. Both DCM and LVNC were included in the same review, because both conditions are still considered idiopathic (6,14) in most patients. Some of the records were further reviewed regarding echocardiographic examinations and results. DCM and LVNC were classified according to the WHO cardiomyopathies classification during the study period. For DCM, left ventricular end-diastolic dimension (LVEDD) had to be ≥ 2 standard deviation (SD) units above normal according to the body surface area of the patient (13,15), and left ventricular fractional shortening (LVFS) had to be $\leq 27\%$ and exhibits symptoms of congestive heart failure. DCM due to structural heart diseases, arrhythmia or cardiotoxic drugs was excluded. For LVNC, the ratio of noncompacted to compacted myocardium had to be $> 2:1$ at the end of systole, and colour Doppler had to show evidence of the flow within the deep intertrabecular recesses and the absence of coexisting cardiac abnormalities (11). The most commonly used technique for diagnosis of LVNC is echocardiography. Other image modalities used for the diagnoses in this study included cardiac magnetic resonance imaging, computed tomography scan and left ventriculography.

Clinical information

Data regarding the patients' medical history included any symptoms of congestive heart failure and delayed physical development in small children with DCM and chest pain, syncope and arrhythmia in older children. We also recorded any history of respiratory and other infections three months before the diagnosis. Information on age, sex and any family history of cardiac diseases was documented. When a first-degree or second-degree relative was affected by primary dilated or noncompaction cardiomyopathy, the

disease was considered to be familial cardiomyopathy. We documented the results of the physical examinations and investigations at diagnosis, including infectious parameters, cardiac enzymes tests, viral serology, metabolic screening tests and genetic tests. We further assessed electrocardiography (ECG), chest radiograms and echocardiograms studies. Echocardiography was performed using a Siemens 512 ultrasound machine (Siemens Corp., California, USA) and GE-Vivid 7 ultrasound machine (General Electric, Wisconsin, USA). We further analysed possible 24-hour ECG monitoring, exercise test from adolescents and young adults, tomography scans and cardiac magnetic resonance studies. The results of cardiac catheterisation and histological data from endomyocardial biopsies were recorded. The date of initial presentation was defined as the first documentation of the left ventricular dilatation and dysfunction in the case of DCM or on a first pathological test results in the case of LVNC. Left ventricle end-diastolic and end-systolic dimensions and left ventricular fractional shortening were digitally obtained by echocardiography motion mode. No autopsy records were included, as we did not match the mortality in this cohort with the Swedish Mortality Registry.

Follow-up

The cohort was followed up from the date of diagnosis by reviewing their medical records every three months during the first year after diagnosis. The cohort was followed up annually until October 31, 2015. Data on transplants and mortality were obtained from the hospital databases and from the Swedish National Population Registry.

Statistical analysis

In the descriptive analysis, we used means and SDs for normally distributed continuous variables and medians and the 25th and the 75th percentiles for continuous variables with skewed distribution. The annual sex-specific incidence rates of DCM and LVNC were calculated by dividing the new cases of disease by the average population of the same sex in western Sweden for each year between 1991 and 2015. For the survival analysis, we applied the Kaplan–Meier method and the endpoint was defined as the date of death, transplant or the last follow-up visit to a paediatric cardiologist, whichever occurred first. Because of the rare events, we combined the endpoints of death and transplants. Statistical analyses were performed with SPSS software version 22 (IBM Corp, Armonk, New York, USA).

The study protocol was approved by the Joint Commission on Ethics of Sahlgrenska University and the University Hospital in Gothenburg, Sweden (Dnr: 895–14).

RESULTS

In total, 69 children (61% males) with DCM were identified. They had a mean age of 7.4, and their ages ranged from one day to 17.9 years. The combined incidence of DCM, including children with neuromuscular diseases and LVNC, was 0.77 (95% CI 0.59–0.96) per 100 000 person years. There were 58

infants, children and adolescents (53% male) identified by the inclusion criteria for idiopathic and familial DCM and for LVNC, rendering an average annual occurrence of dilated and noncompaction cardiomyopathy of 0.62, with a 95% confidence interval (95% CI) of 0.47-0.80 per 100 000 person years. The mean age at diagnosis was 6.5 (one day–17.9 years), and the median follow-up time was 5.2 years. We analysed 11 children with dilated cardiomyopathy associated with neuromuscular diseases separately.

The children with no neuromuscular diseases were divided into five groups according to their aetiology and symptoms (Table 1).

Group A consisted of 30 children (43%) with IDCM (Table 2). In this group, 15 (50%) children were diagnosed before three years of age. The most prominent symptom in small children was failure to thrive, and almost half of the children presented with respiratory viral-like illnesses or dyspnoea. The 15 children who were older than three years of age were more likely to present with dyspnoea, syncope and arrhythmias, and most of them had a systolic murmur and ECG changes, such as left ventricular hypertrophy with strain. Moreover, their chest radiograms showed interstitial pulmonary oedema and cardiomegaly. The LVEDD z-score was $> +2SD$ in 20 children, and of these, 14 children had a z-score $> +4.5SD$. Treatment with short-term or long-term intravenous or oral diuretics was observed in 19/30 (63%) of the children, and 15 (50%) of the children were admitted to the paediatric intensive care unit (ICU) for intravenous inotropic support. During the first six months after diagnosis, 7/30 (23%) of the children in group A were put on extracorporeal membrane oxygenation (ECMO) and three of them subsequently received a left ventricular assist device. Of the seven children who required ECMO, two were weaned from mechanical support, three received transplants, and two died. We found that 8/30 (27%) of the children recovered as they were asymptomatic with normal cardiac function during follow-up. Of the 30

Table 1 Groups of all 69 children (18 years old or younger) diagnosed with dilated or with noncompaction cardiomyopathy according to aetiology (N = 69) in the Western Health Care Region, Sweden, between 1991 and 2015

	n (%)
Children with symptoms at diagnosis	
Idiopathic dilated cardiomyopathy	30 (43)
Familial dilated cardiomyopathy ^a	4 (6)
Various diseases	6 (8)
Children with mild or with no symptoms at diagnosis	
Familial dilated cardiomyopathy detected through family screening	4 (6)
Left ventricular noncompaction cardiomyopathy	14 (20)
Children with neuromuscular diseases	11 (17)

^aFour children with familial dilated cardiomyopathy had symptoms of congestive heart failure at diagnosis, and four children were detected through family screening.

Table 2 Characteristics, presentation, treatment within two weeks after diagnosis, and outcomes of children (18 years old or younger) diagnosed with IDCM (N = 30) in the Western Health Care Region, Sweden, between 1991 and 2015

	n (%) or Median (IQR)
Sex	
Male	12 (40)
Female	18 (60)
Age at diagnosis	
≤ 3 years	15 (50)
> 3 years	15 (50)
Symptoms ^a	
Congestive heart failure	30 (100)
Respiratory viral-like illnesses	16 (53)
Other symptoms (tiredness, palpitation, late development)	20 (66)
Signs	
Heart murmur	21 (70)
Growth retardation	21 (70)
ECG	
Conductions disturbances	12 (40)
Left ventricle dilatation or hypertrophy	16 (53)
Left atrium dilatation	4 (13)
ST-T wave changes	20 (66)
Sinus tachycardia/extra-systole	15 (50)
Chest X-ray	
Cardiomegaly	17 (56)
Vascular congestion	19 (63)
Other Findings	
Positive result viral screening [§]	4 (13)
Genetic mutation (Plakofilin)	1 (3)
Patients with LVEDD z-score $< 4,5$ at diagnosis	16 (53)
Patients with LVEDD z-score $\geq 4,5$ at diagnosis	14 (47)
LV fractional shortening % at diagnosis	19 (9 – 26)
Children with mitral valve regurgitation grade I – III	26 (86)
Admission to ICU	15 (50)
Treatment	
Loop Diuretics/Spirolactone	19 (63)/7 (23)
Digoxin/ACE inhibitor	13 (43)/14 (46)
Aspirin/Anticoagulant	2 (7)/5 (16)
Beta-blocker/Corticosteroid	12 (40)/4 (13)
Selenium/Riboflavin	1 (3)/1 (3)
Interleukin 6/Intravenous gamma globulin	1 (3)/1 (3)
Nasogastric tube/Percutaneous endoscopic gastrostomy	2 (7)
Pacemaker implantation	1 (3)
ECMO/mechanical assist device	7 (23)
Outcomes	
Children who recovered during 25-year study period	8 (26)
Death or transplantation during 25-year study period	7 (23)
Death or transplantation in children ≤ 3 years of age	5 (16)
Death or transplantation in children with LVEDD z-score > 2	7 (23)
Death or transplantation in children with LVEDD z-score $\geq 4,5$	3 (10)

^aBecause symptoms, presentation and treatment may have overlapped, categories add up to more than 100%.[§] Respiratory Syncytial and Human Herpes virus 6 in one child, Respiratory Syncytial virus in one child, Parvovirus in one child and Cytomegalovirus in one child.

children with IDCM, four died and three underwent a heart transplant, including five (17%) who were younger than three years of age at the time of diagnosis. Of the seven children who died or had a heart transplant, only three had an LVEDD z-score of $\geq + 4.5$ SD at diagnosis.

Group B consisted of four children diagnosed with symptomatic familial DCM. These included one died days after being diagnosed at one day of age. There were two children diagnosed at two weeks of age: one required ICU admission and died within two weeks of diagnosis, and the other was admitted to the paediatric cardiology ward and was still alive at when they were followed up three years later. The fourth child was diagnosed at one year of age and was still alive when they were followed up at 20 years of age.

Group C consisted of six children with DCM associated with various diagnoses: two had metabolic disease, one had Holt–Oram syndrome, one had a serious skin disease, one had immune deficiency disease, and one had severe malnutrition. All children in this group were symptomatic at diagnosis and admitted to the paediatric cardiology ward. Three children were admitted to the paediatric ICU and received treatment: one had a pacemaker implanted, all were fed by a nasogastric tube, and all underwent percutaneous endoscopic gastrostomy at a later date. The child with severe malnutrition recovered during the study period. The child with metabolic disease died at the age of one, and the child with immune deficiency disease died at seven years of age.

Group D consisted of four asymptomatic children detected during family screening at 11 and 16 years of

age. Dilatation of both the right and the left ventricle was seen in two of these children, and both were suspected to have arrhythmogenic right ventricular cardiomyopathy. All four children developed symptomatic DCM and later received treatment. None of the children in this group died during the study period.

Group E consisted of 14 children with LVNC diagnosed through family screening or who were found to have cardiac arrhythmia. Only two children in this group had an LVEDD z-score of $\geq + 4.5$ SD. We found that six children with normal cardiac function did not receive any medication during the study period, while eight children received betareceptor blockers to treat them for arrhythmia or were given them as prophylaxis, together with aspirin. Warfarin was given to one child, and another received an implantable cardioverter defibrillator. Development of mild heart dysfunction was observed in two children, but no treatment was initiated during the study period. No child with just LVNC died.

In our cohort, 11 of 69 (16%) children were found to have DCM associated with neuromuscular diseases. All of these children received their cardiomyopathy diagnosis after 10 years of age. They presented with tiredness and congestive heart failure and had an LVEF of $< 27\%$. Within two weeks of diagnosis, eight children were treated with loop diuretics and four children also received additional angiotensin-converting-enzyme inhibitors. Digoxin was given to two children: one received beta receptor blockers, and one received aspirin. Within eight years of diagnosis, five of these 11 children had died. No children from this group were listed for heart transplants.

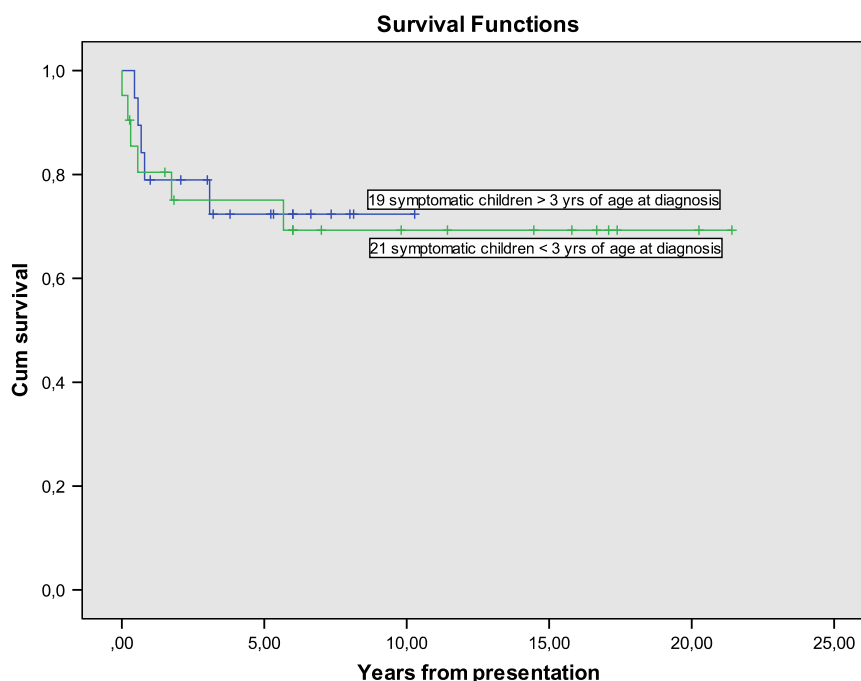


Figure 1 Transplant-free survival in 40 symptomatic children diagnosed with IDCM, familial dilated cardiomyopathy and others various diseases (18 years old or younger) in the Western Health Care Region, Sweden between 1991 and 2015.

The transplant-free survival rates of children with IDCM, familial cardiomyopathy and various other diseases were 79%, 74% and 70% at one, two and five years after diagnosis, respectively (Fig. 1).

DISCUSSION

In this cohort study of DCM and LVNC, we observed an annual incidence of 0.77 (95% CI 0.59–0.96) per 100 000 person years in children of up to 18 years of age. This annual incidence corresponded to two to three children and adolescents with newly diagnosed DCM and LVNC cardiomyopathy each year in western Sweden. These results indicate that a total of eight to 12 new cases are diagnosed annually in this age-specific population in Sweden.

This annual incidence was similar to earlier reports (1,6,16). Other studies have shown that the annual incidence of DCM in children up to 18 years of age was 0.57 (16) and 0.73 (6) per 100 000 person years in North America and Australia, respectively. A nationwide study in Finland carried out between 1980 and 1991 showed an annual incidence of 0.34 per 100 000 person years for idiopathic DCM (13). The higher incidence in our cohort than in the Finnish study may be explained by the inclusion of patients with familial and noncompaction cardiomyopathy. A Swedish register-based study reported that the post-mortem results of 12.2% of children and adults who suffered sudden cardiac deaths between the ages of 15 and 35 showed DCM (8).

Children with neuromuscular and other metabolic diseases were included in our cohort, which may explain the minor differences in incidence rates. In our cohort, as well as in the Finnish and Australian cohorts, the majority of children with idiopathic DCM presented during the first year of life.

The transplant-free survival rate in our study was 79%, 74% and 70% at one, two and five years, respectively. These figures excluded children with LVNC and neuromuscular diseases. The Finnish study reported corresponding rates of 65%, 56% and 51%, respectively (7). In North American and Australian studies, the survival rates were 69% to 72% at one year and 54% to 63% at five years (16,17). The high mortality observed in our study during the first year after diagnosis was similar to previous reports (7,16–18), as so was the gradual decline with time (16,17). In the Finnish study (7), heart transplants were virtually unavailable, yet the mortality pattern was similar when compared to transplant-free survival rates in other studies. The seemingly better transplant-free survival in our cohort may be explained by the inclusion of asymptomatic patients. The outcomes of childhood dilated cardiomyopathy in our study varied greatly and included full recovery as well as death or transplants (17). These findings were in contrast to the findings from adult studies and may imply the need to evaluate different medical treatment protocols and provide indications for heart transplants. In our cohort, mortality later than one year after diagnosis was mainly confined to children with metabolic or neuromuscular diseases.

The diagnosis of children and adolescents with DCM associated with neuromuscular disease is often made at a late stage. Children with neuromuscular disease have not always been included in other cohorts. In the American Paediatric Cardiomyopathy Registry, children with neuromuscular disease seemed to have higher mortality rates, mainly due to a lower rate of transplants (19). Some authors have suggested that older children, over the age of five years, may have a lower rate of transplant-free survival (17), and it has also been suggested that the rate of recovery is higher in younger children (19–21).

The causes of DCM and LVNC are heterogeneous. Because the clinical presentation may be rather unspecific, diagnosis may be delayed, especially in small children. This can obscure a triggering event of heart failure. Viral myocarditis is one of the suggested causes of childhood cardiomyopathies, but the proportion of children who develop DCM after viral myocarditis is unclear (22–24). We found evidence of familial or genetic causes of cardiomyopathy in 32% of our children, including children with familial DCM, children with LVNC and children with arrhythmogenic right ventricle cardiomyopathy. This finding was in agreement with the study by Alexander et al. (20), who reported familial or genetic cardiomyopathy in 27% of children with DCM. Other studies have suggested that this can occur up to 50% of all cases (17,25). Recent advances in genetic and molecular analysis may lead to a better understanding of the underlying causes of the disease, and this is also likely to be true for left ventricular noncompaction. However, we can only speculate to what extent genetic and environmental factors contribute to the cause of the disease, but similarities in observed incidence rates across countries may suggest that environmental factors only play a minor role. Identifying the factors that can predict outcome is difficult, despite the fact that the detection of patients with the poorest prognosis has improved during the latest decade (5).

Strengths and limitations

The strengths of this study include the fact that this was the first cohort that studied the outcomes of children and adolescents with dilated and noncompaction cardiomyopathy in Sweden. We believe that our results contribute to a better understanding of the demographic spectrum of the disease and of the short-term and long-term outcomes of the disease in childhood. This paper presents information that can hopefully be used to plan better healthcare resources for patients with DCM. Limiting the sample to one clinic allowed us to carry out a uniform and meticulous review and provide an overview of these patients. The setting also provided a population-based assessment of the incidence that was unlikely to have been influenced by selection mechanisms. The limitations in our study include the fact that this cohort only reflected the experiences of one paediatric cardiology centre in Sweden and the small number of patients limited the possibilities of performing subgroup analyses and in providing perspectives on a national level.

CONCLUSION

This study demonstrated that the incidence of dilated cardiomyopathy in western Sweden was similar to those observed by previous studies from North America and Australia. Mortality and heart transplants seemed very common in our study, but were somewhat less frequent than in other studies, which may be due to our inclusion of symptom-free children with familial cardiomyopathy who were diagnosed through screening. The high mortality rates emphasises the need for the early and accurate diagnosis of children and adolescents with DCM. A further challenge is to identify children who need transplants as well as children with high potential for spontaneous recovery. Larger population-based studies are needed to better identify prognostic determinants.

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CONFLICT OF INTERESTS

The authors do not have any conflict of interest to declare.

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