Cardiomyopathy in newborns and infants: a broad spectrum of aetiologies and poor prognosis

Badertscher, A C
Cardiomyopathy in newborns and infants:
a broad spectrum of aetiologies and poor prognosis

INAUGURAL-DISSENTATION

zur Erlangung der Doktorwürde der Medizinischen Fakultät
der Universität Zürich

vorgelegt von
Andrea Claudia Badertscher
von Zäziwil BE

Genehmigt auf Antrag von Herrn Prof. Dr. med. F.H. Sennhauser
Zürich 2009
INTRODUCTION
Cardiomyopathy is a disease of the heart muscle characterized by the presence of systolic or diastolic dysfunction or abnormal myocardial structure. The annual incidence is around 8 per 100000 within the first year of life (1). Cardiomyopathies are subdivided into hypertrophic, dilated, restrictive, arrhythmogenic right ventricular and unclassified cardiomyopathies (2).

In infants, cardiomyopathy often forms part of a systemic disease involving multiple organ systems, such as genetic syndromes, metabolic diseases and neuromuscular disorders (3–5).

Progression from the hypertrophic to the dilated form of cardiomyopathy is possible in one and the same patient. There are only a few patients in whom a causal therapy can be initiated. There is little published data about aetiology and clinical courses of cardiomyopathy in infants. Counseling and risk assessment may be difficult due to a lack of knowledge on the clinical course and prognostic factors. This study set out to identify predictors for an adverse outcome by critically assessing the clinical findings, morbidity, mortality and aetiology of all infants with cardiomyopathy, seen at our institution over the last 10 years.

Abbreviations
DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; UCM, unclassified cardiomyopathy.

Patients and Methods
This study is a retrospective analysis in a single tertiary care centre. We included all consecutive infants and neonates with cardiomyopathy diagnosed within the first year of life and born in the years from 1995 to 2004. Patients with secondary cardiomyopathy due to longstanding tachycardia, cardiac surgery or elevated ventricular pressures were excluded from the study.

Patients were divided into five groups: dilated, hypertrophic, restrictive, right ventricular arrhythmogenic and unclassified cardiomyopathies (such as non-compaction) in accordance with the WHO classification (2). Dilated cardiomyopathy (DCM) is characterized by dilatation and/or impaired contraction of the left ventricle or both ventricles (2). A left ventricular end-diastolic dimension of more than 2 standard deviations above the mean normal values (6) was considered as dilated. An ejection fraction of 55% or less or a shortening fraction of 28% or less was regarded as impaired contraction (7). Hypertrophic cardiomyopathy (HCM) was defined by a septal or posterior wall thickness that was more than 2 standard deviations above the mean normal thickness (6).

Patients were subdivided according to aetiology as follows: genetic syndromes, metabolic diseases, neuromuscular disease, familial isolated cardiomyopathy, inflammation and unknown aetiology (8).

The genetic syndromes were subdivided into three groups.
(1) Classified syndrome: the patient shows dysmorphic findings typical of a known syndrome, and genetic analysis...
confirmed the diagnosis. (2) Suspected known syndrome: the patient shows dysmorphic findings typical for a known syndrome, but genetic confirmation was either not feasible (because the responsible gene is still unknown) or no mutation in the gene known to cause the syndrome was detected. (3) Suspected unknown syndrome: the patient shows multiple dysmorphic findings but a recognizable syndrome could not be classified.

Heart failure was defined as severe when catecholamines and/or intubation was required.

The study was approved by the local hospital ethical committee, and written informed consent was obtained for the data collection.

For statistical analysis, we used SPSS 14.0 for Windows. Patient groups were compared using the Mann–Whitney U-test or crosstabs and chi-square test. p-value < 0.05 was defined as significant. Survival was calculated using Kaplan–Meier analysis. Echocardiographic values were compared using the Z score.

**RESULTS**

**Type of cardiomyopathy**

Over the 10-year-period, 35 infants presented with cardiomyopathy. Figure 1 shows the distribution of the cases over the 10 years. DCM and HCM were the two leading types of cardiomyopathy, while restrictive and right ventricular arrhythmogenic cardiomyopathies were not represented (Table 1). Three infants were in the unclassified cardiomyopathy (UCM) group: the first patient fulfilled the criteria for non-compaction (9). Genetic analysis failed to demonstrate a mutation characteristic for Barth syndrome. The second patient showed a small left ventricle with a spongy myocardium and moderately impaired ventricular function. His right ventricle was mildly enlarged and its function mildly impaired. The aetiology remained unknown, and he died at the age of 1 month. The third infant with UCM suffered from long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency. His ventricular myocardium was neither dilated nor hypertrophic but the left ventricular function was severely impaired with a shortening fraction of 17%. He died at the age of 3 days.

**Aetiology**

In 51% (n = 18) of the patients the aetiology of the cardiomyopathy remained unknown. The identified aetiologies (49%) were all genetic (Fig. 2). Genetic syndromes and metabolic diseases are the most frequent aetiologies (Table 2).

---

**Table 1** Demographic data, outcome and symptoms of heart failure in 35 patients with cardiomyopathy

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>DCM</th>
<th>HCM</th>
<th>UCM</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>18</td>
<td>14</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Percentage of all</td>
<td>51</td>
<td>40</td>
<td>9</td>
<td>100</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>1.25</td>
<td>0.27</td>
<td>2.00</td>
<td>0.75</td>
</tr>
<tr>
<td>Age at diagnosis (days): median (range)</td>
<td>28 (0–304)</td>
<td>75 (0–332)</td>
<td>3 (0–148)</td>
<td>26 (0–332)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or transplant: N (%)</td>
<td>8 (44)</td>
<td>4 (29)</td>
<td>3 (100)</td>
<td>15 (45)</td>
</tr>
<tr>
<td>Age at death/transplant (days): median (range)</td>
<td>86 (1–1907)</td>
<td>94 (53–118)</td>
<td>31 (2–520)</td>
<td>85 (2–1907)</td>
</tr>
</tbody>
</table>

| Symptoms of heart failure | | | | |
| Severe heart failure: N (%) | 8 (44.5) | 3 (21) | 3 (100) | 14 (40) |
| Mild or moderate heart failure: N (%) | 8 (44.5) | 6 (43) | 0 (0) | 14 (40) |
| No heart failure: N (%) | 2 (11) | 5 (36) | 0 (0) | 7 (20) |

DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; UCM = unclassified cardiomyopathy.
With DCM, the aetiology remains unknown more frequently than for HCM (66% vs. 29%; \( p = 0.037 \), Table 2). It was possible to assign patients with HCM to a genetic syndrome more frequently.

**Clinical presentation**

Heart failure was the most frequent reason for the first consultation in our cohort (Table 3). Heart failure, if present, was severe in most of the patients and required intubation and/or catecholamines in 25/28 patients during subsequent follow-up. The DCM group had a high heart failure rate (16/18), while more than a third of the patients with HCM (5/14) were without symptoms (\( p = 0.095 \)). A total of 7/35 patients remained free of any heart failure symptoms throughout the duration of the study.

A systolic murmur was present in 25/35 infants at the time of diagnosis. No correlation was found between heart auscultation and the severity, morphology or aetiology of the cardiomyopathy.

**Table 2** Diagnosis, cardiac morphology and age of death or transplant of 35 patients with cardiomyopathy

<table>
<thead>
<tr>
<th>Aetiology of the cardiomyopathy</th>
<th>DCM (N)</th>
<th>HCM (N)</th>
<th>UCM (N)</th>
<th>Age at death/ transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Syndrome Classified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noonan</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Alive</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>1</td>
<td>4 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected known*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noonan</td>
<td>2</td>
<td></td>
<td></td>
<td>Alive</td>
</tr>
<tr>
<td>Costello</td>
<td>1</td>
<td>3.9 months</td>
<td>1</td>
<td>Alive</td>
</tr>
<tr>
<td>Cantu syndrome</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected unknown†</td>
<td></td>
<td>2.7; 3.4 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysmorphic syndrome</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2 days; 3 days; 4.3 months</td>
</tr>
<tr>
<td>Barth syndrome</td>
<td>1</td>
<td></td>
<td>1</td>
<td>2 days; 3 days; 4.3 months</td>
</tr>
<tr>
<td>LOHAD deficiency</td>
<td></td>
<td>1</td>
<td></td>
<td>2 days; 3 days; 4.3 months</td>
</tr>
<tr>
<td>ATP-synthase deficiency</td>
<td></td>
<td>1</td>
<td></td>
<td>2 days; 3 days; 4.3 months</td>
</tr>
<tr>
<td>Defects in complex I and IV of respiratory chain</td>
<td></td>
<td>1</td>
<td></td>
<td>2 days; 3 days; 4.3 months</td>
</tr>
<tr>
<td>Unclassified metabolic disease</td>
<td></td>
<td>1</td>
<td></td>
<td>2 days; 3 days; 4.3 months</td>
</tr>
<tr>
<td>Familial isolated Myopathy</td>
<td></td>
<td>3</td>
<td></td>
<td>1.7 months; alive</td>
</tr>
<tr>
<td>Steinert’s dystrophy myotonica</td>
<td>1</td>
<td></td>
<td></td>
<td>1.7 months; alive</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*Patient shows dysmorphic findings typical for a known syndrome, but genetic confirmation was either not feasible (because the responsible gene is still unknown) or no mutation in the gene known to cause the syndrome was detected.

†Patient shows multiple dysmorphic findings but a recognizable syndrome could not be classified.

ATP = adenosine triphosphate; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LCHAD = long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; UCM = unclassified cardiomyopathy.

Dysmorphic features were present in 16/35 infants. In 13 of these patients, a confirmed or possible genetic aetiology was found (Table 2).

The ECG was normal in only four patients at first presentation and in one at the end of follow-up. The most common pathological finding was an unspecific ventricular repolarization abnormality (20/33). The voltage criteria for ventricular hypertrophy were fulfilled in 15 patients (DCM: 6/16, HCM: 8/11, UCM: 1/5).

The echocardiography at presentation of infants with DCM showed a median ejection fraction of 35% (7%–57%) and a median shortening fraction of 15% (6%–58%). There is a trend towards a lower initial shortening fraction in non-survivors compared with survivors having DCM (15 vs. 20; \( p = 0.48 \)). The size of the left ventricle reached its maximum in most of the patients with DCM within the first year after diagnosis (Fig. 3). In HCM, the median Z score of posterior wall thickness was 3.6 at the beginning (−0.4 to 7.5) and 3.5 (0 to 10.5) at the end of the follow-up. Systolic function, as measured by shortening fraction and ejection fraction, was within the normal range in all patients with HCM. 6/14 patients with HCM had an outflow tract obstruction (5 left and 1 both outflow tracts).

**Outcome**

During a median follow-up time of 1.5 years (range 0–9 years), 13 patients died and 2 underwent heart transplant. Most of the patients died within the first 2 years of life (Fig. 4). There was a trend towards a better survival in patients with HCM (10/14) compared with the DCM group (10/18) (Table 1). In the HCM group, all the patients who died suffered from a syndrome or from general myopathy and three of the four patients who died had an obstructed left ventricular outflow tract. The group of patients with
severe heart failure symptoms within the first month of life had a significantly worse outcome than the rest of the study population (p < 0.0001). All the patients who remained asymptomatic throughout the study period survived. In all 13 patients who died, the cause of death was progressive heart failure. There was a trend towards a worse outcome in patients who were diagnosed early: five of eight deaths from DCM and all four deaths from HCM occurred in patients who were diagnosed within the neonatal period.

**DISCUSSION**

This report gives a detailed picture of the aetiology, clinical pattern, cardiac morphology and outcome of cardiomyopathy in 35 patients diagnosed within the first year of life. In our study population, the frequency of the various morphologies of cardiomyopathy was similar to that reported in other series (10,1). DCM was the most common type, followed by HCM. Restrictive and right ventricular arrhythmogenic cardiomyopathies are rarely diagnosed in infants (10–12) and were not represented in our cohort.

The incidence of HCM is lower when compared with older children or adults (10). This may be explained by the later occurrence of symptoms such as heart failure in HCM compared to DCM (Table 1). The normal thickness of the infant ventricular myocardium also shows a much wider variation range in relation to the size of the heart than in older patients (6). For this reason, it is possible that the true
Cardiomyopathy in newborns and infants

The incidence of HCM in infants is still being underestimated. The existence of a male predominance of 69–75% in HCM (10,4) is also supported by our data.

Finding the aetiology of a cardiomyopathy can be time-consuming and frustrating. The reported success rate is around 30% (13) and it is 50% in our study. Nevertheless, it is important to undertake every effort to establish the aetiology of the cardiomyopathy because there may be a causative therapy available. Also, specific screening of other members of the family and meaningful counselling of the parents regarding the risk of recurrence is possible only if the aetiology of the cardiomyopathy is known. It may also help in forecasting the further course of the disease: in our study population, the clinical course and the age of death of patients with known aetiologies were within the previously published and predicted range for the respective disease in all patients (Table 2) (14–19).

Recently published guidelines may assist in achieving a systematic approach in diagnosing cardiomyopathies (8), and the early involvement of sub-specialists in metabolic, genetic and neuromuscular diseases is helpful in focusing these examinations on clinical suspicion and in keeping costs low. The two leading groups of known aetiologies, namely genetic syndromes and metabolic diseases (Table 2), must always be considered when searching for the aetiology of cardiomyopathy in infants.

In 7 of the 18 patients with unknown aetiologies, myocarditis was suspected but not proved. Neither the patient’s history nor laboratory testing will help prove or exclude myocarditis, which may be the reason for the DCM in many of these patients.

The incidence of sudden cardiac death in patients with diagnosed cardiomyopathy is surprisingly low. It did not occur in our series and is reported to occur in only 1.3% of all paediatric patients listed for heart transplant (20). The true incidence of sudden cardiac death in paediatric patients with cardiomyopathy is not, however, available. Other studies reported an incidence of 1% in children with HCM (4) and 11% in children with DCM (21). Sudden death is the first sign of cardiomyopathy in as many as 3.5% of the patients (22).

To conclude, cardiomyopathy in infants is a very severe disease with unspecific symptoms and a high mortality, especially when presenting in the first month of life. A multidisciplinary approach is recommended as there are various rare aetiologies, which may lead to cardiomyopathy with the two leading aetiologies being genetic syndromes and metabolic diseases. History, clinical examination and laboratory testing will be successful in many patients with HCM and in some patients with DCM.

References

Cardiomyopathy in newborns and infants  

Badertscher et al.  


Curriculum vitae

Andrea Claudia Badertscher

Geburtstag: 30. Dezember 1983
Geburtsort: Zürich
Zivilstand: ledig
Heimatort: Zäziwil, Kanton Bern

Weiterbildung:

Seit 2009 Assistentenstelle Chirurgie Ospedale Regionale di Locarno

Ausbildung:

10/2008 Staatsexamen Universität Zürich
2002 - 2008 Medizinstudium Universität Zürich
02-06/2006 Austauschsemester mit ERASMUS in Italien Università degli studi di Trieste
1998 – 2002 Mathematisch-Naturwissenschaftliches Gymnasium Rämibühl Zürich
1990 – 1996 Primarschule Au-Wädenswil