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Management of children with dilated cardiomyopathy in The Netherlands: Implications of a low early transplantation rate

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BACKGROUND: The policy for listing and transplant for children with dilated cardiomyopathy (DCM) in The Netherlands has been conservative because of low donor availability. The effects of this policy on outcome are reported.

METHODS: This was a multicenter, nationwide study performed in 148 children with DCM. The primary outcome was death or heart transplant.

RESULTS: Overall, 43 patients (29%) died or were transplanted. Within 1 year of diagnosis, 21 patients died, and only 4 underwent transplantation (3 on mechanical circulatory support). The 1-year survival was 85% (95% confidence interval [CI] = 79–91), and 5-year survival was 84% (95% CI = 78–90). Transplantation-free survival at 1 year was 82% (95% CI = 75–88) and at 5 years was 72% (95% CI = 64–80). Within 1 year of diagnosis, with death as the main end-point (21 of 25, 84%), intensive care unit admission (hazard ratio = 2.6, $p = 0.05$) and mechanical circulatory support (hazard ratio = 3.2, $p = 0.03$) were risk factors (multivariable Cox analysis); inotropic support was longer in patients reaching an end-point. At >1 year after diagnosis, with transplantation as the main end-point (15 of 18, 83%), age >6 years (hazard ratio = 6.1, $p = 0.02$) was a risk factor. There were 56 (38%) children who recovered, 50% within 1 year of diagnosis. Recovery was associated with younger age; was similar in patients with myocarditis (43%) and idiopathic disease (41%); and was similar in patients initially admitted to the intensive care unit, admitted to the ward, or treated as outpatients.

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CONCLUSIONS: The transplantation rate in our cohort in the first year was low, with 1-year and 5-year survival rates similar to other cohorts. Our results suggest that a conservative approach to list children for transplantation early after presentation may be justifiable except for patients with prolonged intensive care unit or mechanical circulatory support.
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In children, dilated cardiomyopathy (DCM) is a severe disorder with a poor prognosis.[1] In pediatric studies, transplantation rate in the first year after presentation has been relatively high.[1–3] During a first intensive care unit (ICU) hospitalization, 24% of children with DCM died or underwent heart transplantation[4]; this emphasizes that a decision about transplantation is made early after a first admission for a considerable subgroup of children.

Several studies identified risk factors for the combined end-point of death or transplantation. These include etiology of DCM and age, congestive heart failure, need for inotropic support, and fractional shortening (FS) at diagnosis.[1,3,5–8] An analysis of the Pediatric Cardiomyopathy Registry (PCMR) showed that the median time between presentation with DCM and listing for transplantation was only 1.4 months. Because most children underwent transplantation, these risk factors may reflect the risk of being selected for transplantation, rather than the risk of dying.[5]

In The Netherlands, children with heart failure have been systematically evaluated for heart transplantation since 1998. However, donor hearts have been scarce, and a conservative approach has been used to list children for transplantation early after presentation, resulting in only a few heart transplantations being performed.[9] We investigated whether this approach affected the prognosis of these children.

Methods

The study was approved by the medical ethical committee of the Erasmus Medical Center, Rotterdam, The Netherlands (MEC2013-239). We reviewed patient and echocardiography databases of all 8 pediatric cardiology centers in The Netherlands. Patients (<18 years old at diagnosis) were eligible if they had presented with DCM between January 1, 2005, and December 31, 2010, in a participating center. They were included if they presented with at least 2 of 3 of the following criteria: (1) symptomatic heart failure, (2) severely impaired function (FS ≤25%), and (3) left ventricular (LV) dilation (left ventricular end-diastolic dimension [LVEDD] > +2 *z*-score). DCM could be secondary to myocarditis, familial or genetic disease, anthracycline toxicity, arrhythmias or heart block, neuromuscular or metabolic disease or otherwise be labeled as idiopathic. Children with structural heart defects or Duchenne muscular dystrophy were excluded.

We defined 3 possible outcomes. The first group reached the combined primary end-point of death or heart transplantation during the study period. The second group had ongoing disease and was still meeting the inclusion criteria at the end of the study. The third group recovered before the end of the study. Recovery was defined as FS >25% and LVEDD < +2 *z*-score at the first of 2 consecutive time points. The database was closed on December 31, 2013, and follow-up ended either when the patient reached a primary end-point or at the last available hospital visit.

The first available patient characteristics and clinical parameters (never recorded >2 weeks after diagnosis) were recorded and studied as potential risk factors for outcome. These included growth, echocardiography measurements, duration of hospital stay, and need for inotropic support and mechanical circulatory support (MCS). Growth parameters were transformed into standard deviation scores (SDS) according to Dutch references.[10] Malnutrition was defined as weight-for-height below −2 SDS for children aged >1 year or weight-for-age below −2 SDS for children aged >28 days and <1 year and/or height-for-age below −2 SDS for children aged >28 days. LV dimensions were measured in the parasternal long-axis view. End-diastolic and end-systolic diameters were transformed into *z*-scores using body surface area.[11]

Statistical analysis

Continuous variables are reported as mean (±SD) if normally distributed or otherwise as median with interquartile range (IQR). To calculate incidence rates, population numbers (children 0 to <18 years old) from Statistics Netherlands were used. The Poisson distribution was used to estimate 95% confidence intervals (CIs).

Survival was estimated with the Kaplan-Meier method, and 95% CIs were calculated using Greenwood's formula. The outcomes of death and transplantation were also analyzed by competitive risk analysis. Univariable and multivariable Cox regression were used to find risk factors for the risk of death or transplantation within 1 year of or more than 1 year after diagnosis. All significant ($p < 0.05$) risk factors in univariable analysis were used in the multivariable Cox model. Patients who recovered and patients who did not were compared using univariable Cox regression analysis. Unpaired and paired Student's *t*-tests were used to compare the baseline and follow-up measurements in patients with ongoing disease and in patients who recovered. Testing was performed two-sided, and statistical significance was defined as $p < 0.05$. All analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY).

Results

Baseline characteristics

We included 148 patients; 47% were boys (Table 1). Most patients were hospitalized at presentation; 41% were in the ICU receiving inotropic support, and 37% were in the pediatric ward. There were 12 (8%) patients who needed MCS during first hospitalization. Of patients, 22% were initially treated as outpatients; they had mild symptoms, or surveillance echocardiography was performed because of an underlying condition associated with DCM.

Echocardiography at baseline was available in almost all patients (146 of 148) (Table 2). Diagnosis was made abroad