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Potential for and timing of recovery in children with dilated cardiomyopathy

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ABSTRACT

Objective: Understanding the clinical course and time-frame for recovery is helpful to guide management and counselling following a diagnosis of Dilated Cardiomyopathy (DCM). We aimed to document outcomes and time to recovery for a cohort of patients with a dilated cardiomyopathy phenotype.
Methods: An observational cohort methodology was used to collect retrospective data from the departmental database for those identified with DCM. Data relating to mode of presentation, echocardiographic parameters, clinical management and outcome were collated and analysed. Predictors and time-scale for recovery were investigated and reported.
Results: 209 new referrals were included within the time frame. 82 children median age 1.0 years (IQR 3.4) required intensive care (ICU) and their survival without death or transplant was 51% to one year and 45% to five years. 127 children presented to the pediatric heart failure clinic. Excluding 58 with neuromuscular disease, median age was 4.1 years (IQR 11.3) & survival without death or transplant 85% to 1 year and 50% to 5 years. NT-proBNP normalized in survivors before echocardiographic parameters. Predictors of recovery included younger age, female sex and smaller left ventricular end diastolic *Z* score on echocardiogram at presentation.
Conclusion: Transplant-free survival to one year is significantly better for patients presenting to clinic, but longer-term survival is better amongst those presenting to ICU due to a late attrition in those with less severe heart failure at presentation. Falling NT-proBNP is the earliest marker of recovery. Recovery of cardiac function remains possible up to three years from presentation.

1. Introduction

Our understanding of the epidemiology of pediatric DCM is well served with good databases from the United States of America and Australia [1,2]. However, while there is striking similarity in incidence, despite variation in inclusion criteria, the data on the rates of death, transplant and recovery of function are discrepant between these 2 major registries.

The highest risk period in both datasets is the first year after presentation and transplant-free survival is similar at 74% and 69% respectively [3,4]. However for children requiring hospitalization for a first episode of heart failure, a single center study from America has shown transplant-free survival to be only 46% at 1 year, whereas registry data from the UK showed a transplant-free 1 year survival of 66% [5,6]. While congestive heart failure is common in pediatric DCM and its presence increases the hazard for death, the severity has not been specifically addressed as a risk factor [4]. Recent Dutch registry data has shown transplant-free 1 year survival of 82% and suggested rather controversially "a conservative approach [to transplant listing], specifically in young children presenting with heart failure and requiring ICU admission, but not mechanical circulatory support, is justifiable" [7].

We aimed to provide further data on outcomes based on severity of presentation by using a surrogate evaluation relating to mode of presentation. We hypothesised that children presenting to an ambulatory clinic or low dependency inpatient setting versus those decompensated to the intensive care would have different outcomes in their clinical progress in the short and medium term from presentation. We were also interested in determining the outcomes for those patients who recovered following their initial presentation and whether any improvement was sustained. This detailed information from a single centre would be useful for pediatric cardiologists to be aware of when faced with families and children with new onset DCM. Therefore, we reviewed the data from a large pediatric heart failure program and compared the outcomes for children admitted to the ICU with those who presented less acutely, over a 5 year period. For those that survived without a transplant we investigated the proportion and timescale for recovery of clinical parameters with particular attention

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to the role that routine measurement of NT-proBNP might add to our predictive ability.

2. Materials and methods

Great Ormond Street Hospital is a tertiary and quaternary pediatric referral center accepting patients from district general hospitals in the South East of England, and from other pediatric cardiac units across the UK. This study complies with the declaration of Helsinki and received approval from the local research governance department.

We evaluated all children ≤16 years with primary or secondary DCM who were referred to our unit between January 2008 and July 2013 inclusive. Follow up data were included if individuals had a minimum of two episodes of care. Follow up was censored at the most recent known point of follow up.

A DCM phenotype was diagnosed on 2 dimensional echocardiography. All patients included in this study had a fractional shortening (FS) measurement of ≤26% at presentation and a left ventricular end diastolic dimension (LVEDD) *Z* score of >+2. Patients were divided into two groups according to severity of presenting features; those who required admission to the cardiac ICU, and those who were managed in the outpatient clinic or a low dependency ward setting. For all patients in addition to the echocardiographic measurements above we recorded the NYHA/Ross score, NT-proBNP levels, and for ward/clinic patients' medications used.

Between-group comparisons were made using unpaired Student *t*-test or Mann–Whitney *U* test as appropriate to the underlying distribution of the variables. A curve demonstrating the proportions of patients who died, were transplanted or remained alive without transplant over time was created to graphically demonstrate the patients' outcomes.

Survival curves using Kaplan–Meier methodology censored for patients with a combined end point of either death or transplant were created and censored at the time of most recent follow up. Survival outcomes comparing patients who presented to intensive care versus those who presented to a low dependency or ward environment were compared using the log-rank test.

A series of univariate Cox regression analyses were then performed to identify the risk of either death or transplant attributable to individual variables. Variables with a p value <0.1 were included in the subsequent multivariate analysis. To provide clinical relevance a change in NT-proBNP of 1000 pg/ml was considered to be clinically relevant with the absolute value divided by 1000.

For those children who remained event free, without death or transplant, we evaluated whether the shortening fraction (FS), the ventricular size (LVEDD *Z* score) or NT-proBNP returned to the normal range. Using time to recovery for each of these variables and defining overall recovery as return to normal of all three clinical parameters, Kaplan–Meier analysis was used to construct an inverse survival curve to graphically represent the probability of recovery and the recovery time for each of the variables as well as the composite end point of all three parameters to provide overall recovery.

Cox regression analysis was used to identify individual variables that significantly predict recovery. Variables with a p value <0.1 were carried forward to a subsequent multivariate analysis.

Sources of bias were considered due to patients being seen by different clinicians for follow up. Measurement bias on echocardiography was limited by use of a departmental protocol though studies were performed by multiple operators.

3. Results

Within the five year timeframe there were 209 new referrals for pediatric patients with a DCM phenotype. Of these 82 children, median age 1.0 year (IQR 3.4), were admitted to the cardiac intensive care unit and 12 (15%) of these were clinically diagnosed with myocarditis. Cardiac biopsy is not routinely undertaken to diagnose myocarditis in the UK and the rationale for this has been described previously [6]. Mechanical support was needed with ECMO or Berlin Heart in 28 (34%) and transplant in 29 (35%). Survival without death or transplant was 51% to one year and 45% to five years. All the patients presenting to intensive care were in NYHA class III or IV and distributed across the NYHA classification for children in low dependency settings. Patient details are included in Table 1.

During the same period 127 new referrals were seen in the pediatric heart failure clinic or admitted to a low dependency ward with AHA/ACC heart failure stages B and C. Of these 58 had neuromuscular disease with reduced FS and 3 died within a year of presentation. Neuromuscular patients were excluded from the subsequent analysis.

Of the remaining 69 new patients with DCM seen in low dependency settings the median age was 4.1 (IQR 11.2) and 3 (4.3%) were clinically diagnosed with myocarditis. Oral anti-failure medication was used to support cardiac function. The following drugs were used at any time point during follow up. Either angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) were used in all patients (ACEI in 96%, ARB in 4%), Furosemide in 78%, Spironolactone in 74%, Warfarin in 9%, Aspirin in 54%, Betablocker (Carvedilol) in 65%, and Digoxin in 56%. 4 patients received Ivabradine, 2 patients Carnitine and 1 patient received Sildenafil. Survival without death or transplant for these patients was 85% to 1 year, and was 50% to 5 years.

The different transplant-free survival between those children presenting to intensive care and those to a low dependency setting is shown in Fig. 1A.

Assumptions for proportional hazards modelling were met with no significance demonstrated due to changes over time. Multivariate modelling for predictors of death or transplant for all patients despite their location of presentation is shown in Table 2.

Older age, reduced FS at presentation and increased NT-proBNP level per 1000 unit increase were significant risk factors. LVEDD *Z* score at baseline was not a significant predictor of outcome. Whilst presenting to the intensive care unit was a significant risk factor for death or heart transplantation as part of univariate analysis there was no contribution to the multivariate model.

For the 87 patients from both groups who survived without transplant, the time course of recovery is shown in Fig. 1B. NT-proBNP improved before FS, and LVEDD was the last to improve. Recovery was most rapid in the first year after presentation but continued over the subsequent 3 years before entering a plateau phase indicating recovery of biomedical and echocardiographic parameters in 60% of patients. Table 3 documents the predictors for recovery for children presenting in clinic, with young, female children with a smaller left ventricular end diastolic diameter *Z* score more likely to recover their parameters to within the normal range.

4. Discussion

While it is clear that the first year after presentation poses the highest risk in pediatric DCM, this paper shows clear divergence in 1 year transplant-free survival for children with DCM presenting to the ward or clinic (85%) and those needing initial intensive care (51%) [5,6]. This distinction is useful additional information when counselling families, using the 'route of care' as a surrogate for disease severity stratifies the presentation of DCM and provides more granularity regarding prognosis for different modes of presentation. Unlike other cohorts our data includes NT-proBNP which whilst contributing to the model failed to produce a clinically important hazard ratio during univariate or multivariate analysis. However for those patients who recovered the NT-proBNP serial data was clinically useful. NT-proBNP is the first parameter for recovery and when measured serially seems to be an important clinical marker to guide therapy. Further long-term analysis will be useful to answer this question over time. Other predictors of

Table 1
Patient details.

	ICU	Ward/Clinic	*P* value
Number presented	82	69	
Mean age at presentation in years (SD)	3.2 (4.5)	6.3 (5.6)	<0.001*
Median age at presentation (IQR)	1.0 (3.4)	4.1 (11.2)	<0.001*
Number of males (%)	40 (49%)	32 (46%)	0.87
Mean NT-proBNP (SD)	19,460 (12,459)	5609 (8208)	<0.001*
Mean LVEDD *Z* score (SD)	5.3 (4.0)	5.6 (3.5)	0.57
Mean FS % (SD)	13.3 (6.2)	18 (8.1)	<0.001*
Number required mechanical support (%)	28 (34%)	8 (12%)	0.001*
Number transplanted (%)	29 (35%)	12 (17%)	0.01*
Number died (%)	14 (17%)	9 (13%)	0.49
Number in NYHA class I (%)	0 (0%)	41 (59%)	
Number in NYHA class II (%)	0 (0%)	12 (17%)	
Number in NYHA class III (%)	7 (9%)	9 (13%)	
Number in NYHA class IV (%)	75 (91%)	7 (9%)	

* $P < 0.05$.