Cardiology in the Young (2012), **22**, 293–300
doi:10.1017/S1047951111001442

Original Article

Anaemia is a predictor of early death or cardiac transplantation in children with idiopathic dilated cardiomyopathy

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Abstract *Introduction:* The aim of our study was to establish the prevalence and the prognostic value of haematological abnormalities in children with cardiac failure. *Patients and methods:* A series of 218 consecutive children with a first diagnosis of idiopathic dilated cardiomyopathy were retrospectively examined. Haematological evaluation was performed at first diagnosis. Death or cardiac transplantation was the main outcome measure. *Results:* The median age was 0.6 years, ranging from 1 day to 15.8 years and median follow-up was 2.65 years, ranging from 0 to 17.2 years. After a median interval of 0.2 years, ranging from 0 to 8.7 years, 56 patients died and 25 were transplanted. Event-free survival at 1 and 5 years was 68% (95% confidence interval, 63–75%) and 62% (95% confidence interval, 56–69%). Blood levels of haemoglobin less than 10 grams per decilitre, urea over 8 millimoles per litre, and C-reactive protein over 10 milligrams per litre were found in 24%, 20%, and 24% of patients, respectively. The log-rank test showed that haemoglobin ($p = 0.000$) and C-reactive protein ($p = 0.021$) were predictors of death or transplantation. In the multivariate Cox model, haemoglobin (hazard ratio = 0.735; confidence interval = 0.636–0.849; $p = 0.000$) and urea (hazard ratio = 1.083; confidence interval = 1:002–1:171; $p = 0.045$) were predictive of poor outcome. Cubic spline functions showed that the positive role of haemoglobin on survival was linear for values less than 12 grams per decilitre and null for values more than 12 grams per decilitre. Adaptive index models for risk stratification and Classification and Regression Tree analysis allowed to identify the cut-off values for haemoglobin (less than 10.2 grams per decilitre) and urea (more than 8.8 millimoles per litre), as well as to derive a predictor model. *Conclusions:* In children with idiopathic dilated cardiomyopathy, anaemia is the strongest independent prognostic factor of early death or transplantation.

Keywords: Haemoglobin; cardiac failure; myocardiopathy

Received: 1 March 2011; Accepted: 23 August 2011; First published online: 13 October 2011

DILATED CARDIOMYOPATHY, A MYOCARDIAL DISORDER characterised by a dilated left ventricular chamber and systolic dysfunction, is the most common form of cardiomyopathy in children.[1] According to the Paediatric Cardiomyopathy Registry, it is a rare disease affecting 1.13 per 100,000 children.[2–4] It has a constant annual incidence, varying from 0.57 to 0.74 per 100,000 children.[4] The mortality is high, being 30% at 1 year and ranging from 36% to 66% at 5 years.[4]

Various clinical, radiographic, and echocardiographic parameters – such as age, functional class at diagnosis, cardiothoracic ratio, left ventricular fractional shortening, and the degree of mitral insufficiency – have been identified by several authors as risk factors of morbidity and mortality.[4,5] However, these indices have a poor prognostic

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capability, and thus medical treatment is still aimed at treating congestion or low cardiac output.

In adults with cardiac failure, haematological anomalies – such as anaemia,[6,7] neutropenia, lymphopenia,[8,9] increased blood levels of C-reactive protein,[10,11] and urea[7,12,13] – are sensitive predictor factors of morbidity and mortality. Haematological abnormalities are frequently found in children with dilated cardiomyopathy and cardiac failure; however, they are generally attributed to concomitant morbidity, such as renal insufficiency, malnutrition, or infections.

There are no data on the prevalence of haematological anomalies in children with idiopathic dilated cardiomyopathy and their possible impact on prognosis. The aim of this study was to evaluate the prevalence and the prognostic value of haematological abnormalities in a series of 218 consecutive children with idiopathic dilated cardiomyopathy.

Materials and methods

From January, 1990 to December, 2009, we sampled 218 consecutive children with a first diagnosis of idiopathic dilated cardiomyopathy at Necker Enfants Malades, Paris.

Dilated cardiomyopathy was defined as a dilated left ventricular chamber – more than 2 standard deviations – and depressed systolic function, with fractional shortening less than 25%. We included patients only with idiopathic dilated cardiomyopathy, in the age group of 0–16 years.

Exclusion criteria included dilated cardiomyopathy of known and treatable origin, due to neuromuscular disorders, associated with malformation syndrome, due to inborn errors of metabolism, due to Kawasaki disease, or toxic dilated cardiomyopathy. Patients with concomitant infection, fever, or those having received a blood transfusion during the month preceding the diagnosis of dilated cardiomyopathy were also not included. Only blood tests at diagnosis, all performed at the laboratory of Necker Enfants Malades, were taken into consideration, which included haemoglobin, blood cell count, coagulation state, hepatic and renal function, carbon-reactive protein, lactates, sodium, potassium, and blood gas analysis.

Liver insufficiency was defined as blood levels of glutamic oxaloacetic transaminase over 110 international units per litre, of glutamic pyruvic transaminase over 30 international units per litre, of bilirubin over 20 millimoles per litre, associated with International Normalised Ratio over 1.4, prothrombin time less than 80%, coagulation time over 150%, and factor V less than 80%. Renal insufficiency was defined as blood levels of urea over 8 millimoles per litre, of creatinin over 90 millimoles per litre, and of potassium over 4 millimoles per litre. Metabolic acidosis was defined as pH less than 7.2, base excess over −10, and lactates over 2.5 millimoles per litre.

The duration of follow-up was defined as the period between the diagnosis of dilated cardiomyopathy and the occurrence of death or cardiac transplantation. In our institution, patients were put in a waiting list for cardiac transplantation when they had at least two episodes of congestive cardiac failure or low cardiac output with the need for inotropic support. They were put in an urgent list when they needed mechanical ventilation or extracorporeal circulation.[14]

Statistical analysis

Continuous variables were presented as mean plus or minus standard deviation or as median value and range. Categorical variables were presented as frequency and percentage. Relationships between categorical variables were tested using the chi-square test or the Fisher exact test, when appropriate. Relationships between continuous and categorical variables were tested using the Student t test or the Wilcoxon signed-rank test, when appropriate. Correlations between the different biological variables were assessed using the Pearson correlation coefficient r. Event-free survival was the time interval between the date of diagnosis and the date of death, the date of cardiac transplantation or the date of last follow-up. Survival distributions were examined using the Kaplan–Meier test. Risk factors for death or cardiac transplantation were identified using the log-rank test. A two-sided p-value of 0.05 or less was considered statistically significant. A p-value less than 0.05 at univariate analysis was retained to enter a multivariate Cox proportional hazard regression model aimed to identify potential predictive factors of death or cardiac transplantation. All statistical tests were bilateral. The assumption of proportionality was tested using the Schoenfield residuals. A procedure of model selection was applied utilising the Akaike information criteria associated with a Bootstrap approach.[15] To evaluate a possible non-linear relationship between continuous predictors and survival, we have applied cubic spline functions.[16] As a sensitive analysis to identify cut-off values for predictors, we used the Classification and Regression Tree analysis, which is a technique based on recursive partitioning analysis. Unlike multivariable logistic regression, it is suited to the generation of clinical decision trees.

All analyses were performed using the R version 2.11.0 statistical package. The study was approved by the local ethics committee. The parents of the children gave their written consent for the study.

https://doi.org/10.1017/S1047951111001442 Published online by Cambridge University Press

Results

Descriptive analysis

Table 1 shows the descriptive analysis of clinical and biological characteristics of patients at the time of diagnosis. No child had severe malnutrition (less than 2 standard deviations) at diagnosis.

Mean cardiothoracic ratio was 0.64 plus or minus 0.06. Arrhythmias and conduction anomalies were relatively rare. There was one patient with ventricular tachycardia, three with ventricular ectopic beats, six with supraventricular arrhythmias, and one patient with grade 1 atrioventricular block. The mean left ventricular end-diastolic diameter, expressed as a z-value, was 3.74 plus or minus 1.20; and over 4 in 87 patients (40%). Median fractional shortening was 15%, ranging from 5% to 25%, and lower than 20% in 142 patients (65%). Moderate-to-severe mitral regurgitation was found in 68 patients (31%).

The median age at diagnosis was 0.6 years, ranging from 1 day to 15.8 years. The median number of new cases per year was 12, ranging from 2 to 20 years. No child had severe malnutrition. Increased blood levels of urea – over 8 millimoles per litre, C-reactive protein – over 10 milligrams per litre, and decreased blood levels of haemoglobin – less than 10 grams per decilitre – and sodium – over 135 millimoles per litre – were found in 20%, 24%, 24%, and 24% of patients, respectively. Anaemia was found in 54% of patients who died or underwent cardiac transplantation. Neutropenia and lymphopenia were found in only 7% and 2% of patients. Liver insufficiency was found in three patients, renal insufficiency in three, and metabolic acidosis in five patients.

Table 2 shows the descriptive analysis associated with the log-rank test. Age at diagnosis – less than 6 months, blood levels of urea – over 8 millimoles per litre, blood levels of C-reactive protein – over 10 milligrams per litre, and haemoglobin levels – less than 10 grams per decilitre were associated with the occurrence of death or cardiac transplantation, whereas sodium levels – less than 135 millimoles per litre – were not. There was no correlation between blood levels of haemoglobin and urea ($p = 0.2$) or creatinin ($p = 0.1$), ruling out a possible effect of impaired renal function on haemoglobin levels. We did not find the physiological linear relationship between the age at diagnosis and haemoglobin levels ($p = 0.6$).

Follow-up

Patients were followed up for a median period of 2.65 years, ranging from 0 to 17.2 years. The median number of hospitalisations per patient due to cardiac failure was 1, ranging from 1 to 9. A total of 87 patients were hospitalised at least two times for

Table 1. Descriptive analysis of the whole population.

Parameters	n	
Age (years)	218	0.20, **0.60**, 1.70 (2.11 ± 3.60)
Age (months)	218	2.46, **7.54**, 20.65 (25.37 ± 43.24)
Sex (female)	218	49% (106)
Weight (kg)	218	5.40, **8.20**, 11.40 (11.20 ± 10.80)
Presence of oedemas	218	95% (207)
Presence of hepatomegaly	218	75% (163)
Presence of low cardiac output	218	20% (43)
Haemoglobin (g/dl)	218	10.10, **11.40**, 12.40 (11.39 ± 1.73)
Hematocrit (%)	218	31.20, **34.20**, 37.20 (34.50 ± 4.90)
Globular volume (μ^3)	218	77.00, **82.00**, 86.00 (82.67 ± 9.73)
Neutrophils (µl)	185	2943, **4636**, 6903 (5569 ± 3636)
Lymphocytes (µl)	185	3036, **4312**, 6342 (4880 ± 2606)
Carbon-reactive protein (mg/l)	218	5.00, **6.00**, 10.00 (13.10 ± 20.10)
Urea (mmol/l)	218	4.03, **5.70**, 7.50 (6.14 ± 2.86)
Creatinin (mmol/l)	218	38.00, **45.00**, 54.00 (48.80 ± 18.50)
Sodium (mmol/l)	218	135.00, **137.00**, 139.00 (136.56 ± 4.29)
Potassium (mol/l)	218	4.00, **4.40**, 5.00 (4.50 ± 0.68)
GOT (IU/l)	218	28.20, **37.50**, 51.80 (65.30 ± 177.2)
GPT (IU/l)	218	20.00, **31.00**, 43.00 (56.70 ± 162.50)
Bilirubin (mmol/l)	218	8.00, **12.00**, 16.80 (16.30 ± 28.20)

GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase
n is the number of non-missing values
a, b, c represent the lower, median, and upper quartile for continuous variables
(x ± s) represents mean ± 1 standard deviation
Numbers after percent are frequencies

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Table 2. Descriptive analysis, baseline parameters, and prognostic factors of death or cardiac transplantation at univariate analysis – log-rank test.

	IQ	Median	IIIQ	x ± 1.96SD	p-value
Age (months)	2.46	7.54	20.65	25.37 ± 43.24	0.028
Urea (mmol/l)	4.03	5.70	7.50	6.14 ± 2.86	0.178
CRP (mg/l)	5.0	6.0	10.0	13.1 ± 20.1	0.021
Haemoglobin (g/dl)	10.10	11.40	12.40	11.39 ± 1.73	0.000

CRP = carbon-reactive protein; IQ = lower quartile; Median = median quartile; IIIQ = upper quartile for continuous variables

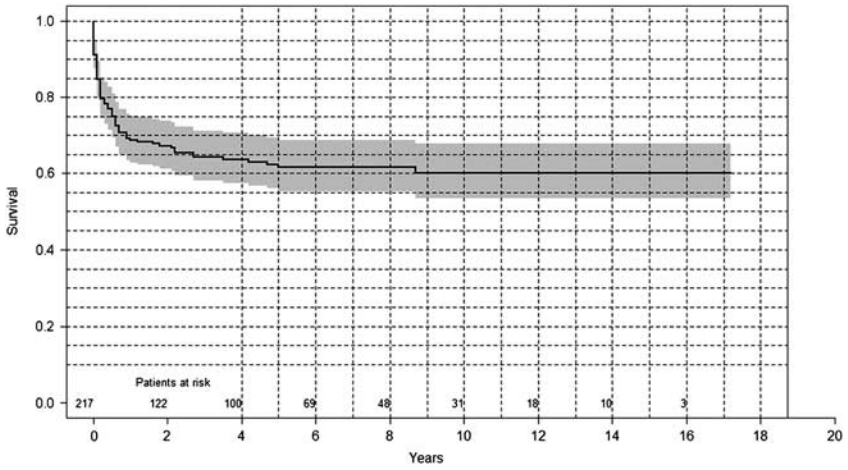

Figure 1.
Survival curve of the whole study cohort. Event-free survival at 1 and 5 years was 68% (95% confidence interval, 63–75%) and 62% (95% confidence interval, 56–69%).

relapse of cardiac failure. Cerebral events occurred in four patients. Death occurred in 56 patients at a median interval of 0.2 years, ranging from 0 to 8.7years, from diagnosis. Within 12 months from diagnosis, 47 patients (84%) died; a total of 61 patients were put on a waiting list for cardiac transplantation, which was performed in only 25 patients at a median interval of 0.5 years, ranging from 0 to 2.2 years, from diagnosis. In all, 18 patients died on a waiting list for cardiac transplantation. The mean age of transplanted patients was 28 plus or minus 48 months. Of the 25 transplanted patients, 15 were younger than 1 year of age.

Death was due to refractory cardiac failure in 42 patients, due to sudden death in 13, due to ventricular arrhythmia in three patients, and from a cerebral event under extracorporeal circulation in one patient.

Figure 1 shows the survival curve for the whole cohort. Event-free survival was 68% (95% confidence interval, 63–75%) at 1 year and 62% (95% confidence interval, 56–69%) at 5 years. Approximately 84% of the deaths occurred within 12 months from diagnosis.

Prognostic factors

Tables 3 and 4 show the results of multivariate analysis. Cox models without selection (Table 3) show that blood levels of haemoglobin are highly predictive of a poor outcome, whereas the predictor power of increased blood levels of carbon-reactive protein is lower. Akaike information criteria selection confirms the strong prognostic value of blood levels of haemoglobin, does not confirm the prognostic value of blood levels of carbon-reactive protein, and shows a low predictor power for increased blood levels of urea (Table 4). An increment of haemoglobin blood levels by 2.3 grams (I–III quartile) decreases the risk of negative outcome by 50%. An increment of urea blood levels by 3.47 grams (I–III quartile) increases the risk of negative outcome by 130%. We did not find a predictive role for very low fractional shortening or severe left ventricular dilatation.

In Figure 2, cubic spline for haemoglobin levels shows that the positive role of haemoglobin on survival is not linear for values less than 12 grams per decilitre and that it is null for values over

https://doi.org/10.1017/S1047951111001442 Published online by Cambridge University Press

Table 3. Prognostic factors of death or cardiac transplantation at multivariate analysis: Cox model without selection.

	HR	Lower 95% CI of HR	Upper 95% CI of HR	p-value
Haemoglobin (g/dl)	0.734	0.635	0.849	0.000
Urea (mmol/l)	1.000	0.990	1.010	0.652
CRP (mg/l)	1.083	1.002	1.171	0.047

CI = confidence interval; CRP = carbon-reactive protein; HR = hazard ratio

Table 4. Prognostic factors of death or cardiac transplantation at multivariate analysis: Cox model after AIC selection.

	IQ	IIIQ	HR	Lower 95% CI of HR	Upper 95% CI of HR	p-value
Haemoglobin (g/dl)	10.100	12.4	0.49	0.35	0.68	0.000
Urea (mmol/l)	4.025	7.5	1.32	1.00	1.73	0.045

AIC = Akaike information criteria; CI = confidence interval; HR = hazard ratio; IQ = lower quartile; IIIQ = upper quartile for continuous variables

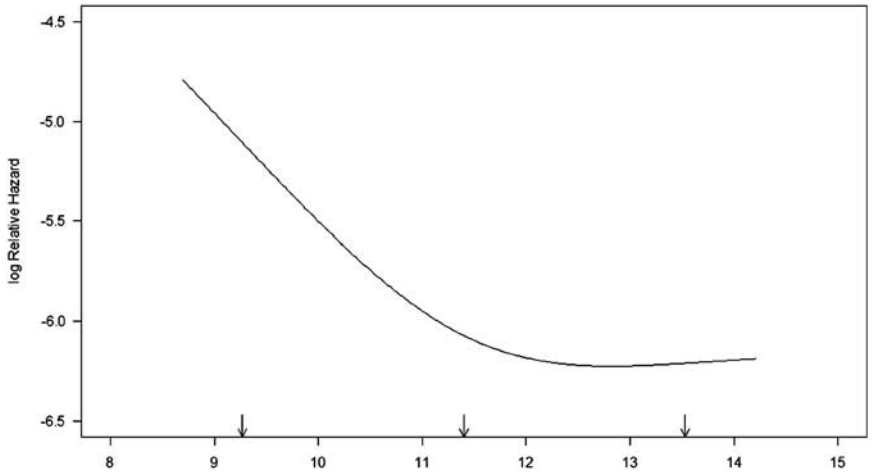

Figure 2.
Relationship between haemoglobin and survival (log Relative Hazard). Cubic spline functions showed that the positive role of haemoglobin on survival was linear for values less than 12 grams per decilitre and null for values over 12 grams per decilitre.

12 grams per decilitre. Classification and Regression Tree analysis confirms that only blood levels of haemoglobin are predictors of poor outcome (Fig 3) and shows that the survival probability at 5 years is only 36% in patients with haemoglobin levels less than 10 grams per decilitre and higher than 70% in patients with haemoglobin levels over 10 grams per decilitre.

We then tried to establish cut-off values for variables associated with poor outcome. An adaptive index model for risk stratification attributes a score of 1 for haemoglobin values lower than 10.2 grams per decilitre, or urea levels higher than 8.8 millimoles per litre, or age at diagnosis younger than 18 months. In an effort to enhance the clinical applicability of these results, a prediction model of death or transplantation was derived. Figure 4 shows a plot of prediction scores versus probability of adverse events.

Discussion

Our study shows for the first time, that in children with idiopathic dilated cardiomyopathy anaemia is very frequent; it is not related to renal insufficiency and is a strong independent prognostic factor of early death or transplantation.

Although in adults with cardiac failure the presence of haematological anomalies has been known for 30 years,[6–10] their existence has not been investigated in children. The prevalence of anaemia in adults with cardiac failure varies from 4% to 55%. Haemoglobin levels are associated with brain natriuretic peptide levels, but are not associated with

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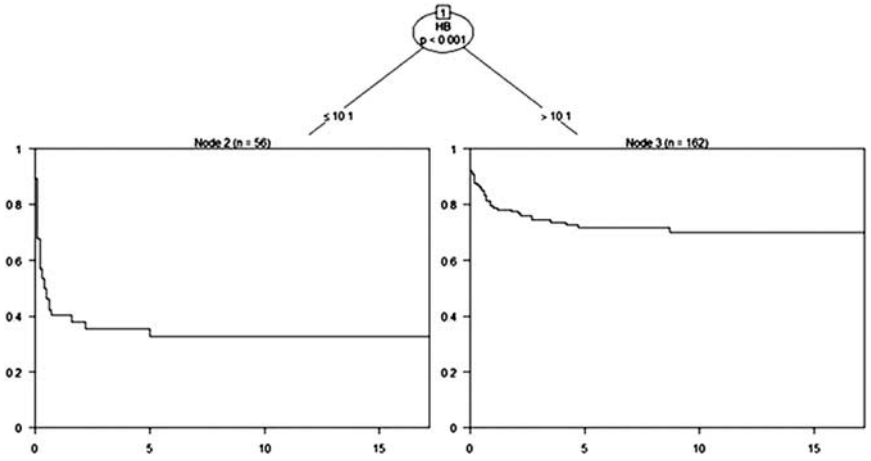

Figure 3.
Classification tree for blood levels of haemoglobin, C-reactive protein, and urea. Only haemoglobin is a predictor of survival in this model. The survival probability at 5 years is 36% in patients with haemoglobin levels less than 10 grams per decilitre and higher than 70% in patients with haemoglobin levels over 10 grams per decilitre.

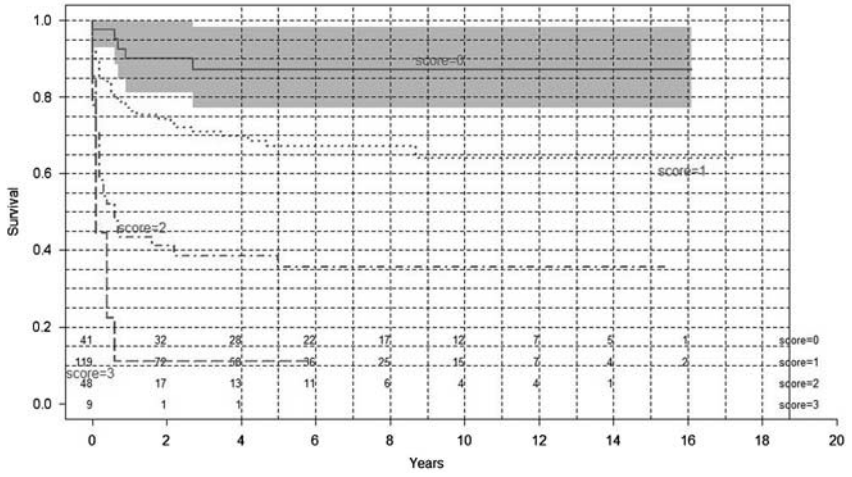

Figure 4.
Prediction model based on adaptive index models for risk stratification. The survival probability at 2 years decreased for 90% (score 0) to 10% (score 3).

erythropoietin levels, or with severity of renal insufficiency.[7] These anaemic patients often have lymphopenia, that is, in 8 out of 10, which is also a prognostic factor of early mortality.[9,10]

In our series, anaemia was present in one-fourth of the patients, and it was a powerful and independent risk factor of early death or transplantation. Univariate, multivariate, Classification and Regression Tree analysis, all indicated that haemoglobin levels were related to survival. Cubic spline functions showed the non-linearity of the relation haemoglobin versus survival for haemoglobin levels inferior to 12 grams per decilitre. The presence of anaemia was not related to age or increased levels of urea, ruling out a secondary effect of renal insufficiency on haematopoiesis. Even if multivariate analysis showed that increasing haemoglobin levels by 1 gram improved the survival probability by 36%, we do not know whether the treatment of anaemia would improve the survival of patients at risk or whether the presence of anaemia only reflects the severity of the disease. Anaemia was not related to neutropenia or lymphopenia, ruling out a global depressive effect on bone marrow by circulating cytokines in children with dilated cardiomyopathy, as it has been suggested in adults with cardiac failure.[17] However, neutropenia and lymphopenia were rare events in our study cohort, probably because of the fact that the duration of the disease in our patients was much shorter that life expectancy of adults with cardiac failure.

No studies have investigated the possible activation of inflammatory indices or the presence of

https://doi.org/10.1017/S1047951111001442 Published online by Cambridge University Press

initial renal dysfunction in children with cardiac failure. Even if in our series children with concomitant infection or fever were excluded and overt renal insufficiency was rare, increased blood levels of C-reactive protein and urea were found in a large percentage of patients.[18] Children with either increased blood levels of urea or carbon-reactive protein had a poorer survival compared with children with normal urea or carbon-reactive protein. However, C-reactive protein was a predictor of poor outcome only at univariate analysis, whereas multivariate analysis showed that only serum urea was a significant predictor of long-term survival.

A major difference between children and adults with cardiac failure is the duration of the disease, which can be extremely short in children.[19,20] Our study cohort was very young, with 63% of patients younger than 1 year of age and 83% younger than 3 years. Death was very frequent and occurred early after the diagnosis. In addition, the majority of deaths occurred in young patients in whom, because of the lack of organs, cardiac transplantation is a remote possibility. Only a minority of patients were transplanted and a large number died on a waiting list. Of the 81 children who died or had cardiac transplantation, 68 were younger than 18 months of age. The survival probability reported in our series was lower than that published by other authors.[4] In one of the first studies on children with dilated cardiomyopathy, the authors, concerned by the high mortality rate of this population, proposed an aggressive treatment of the disease.[21] In other series, including older children, survival was generally higher.[22,23] Similar to us, several authors observed that the majority of deaths occurred between 2 months and 2 years after diagnosis.[23,24] Thus, in children it is extremely important to identify those at risk in order to start an aggressive medical treatment, possibly treating anaemia and/or immediately putting them on a waiting list for transplantation.

Many authors have tried to identify predictors of poor outcome in children with dilated cardiomyopathy for 20 years. However, these studies provide variable findings. Severity of dysfunction has been found to be predictive of outcome in some studies,[25] but not in others.[26] Similarly, the presence of arrhythmia has and has not been associated with a greater risk of death.[25] Younger age at presentation has been reported to be associated with both a better outcome[5] and a worse outcome,[25] or to bear no relation to outcome.[26] Symptoms appear to provide poor prognostic capability because even asymptomatic patients with incidental discovery of dilated cardiomyopathy can have a poor prognosis.[25] In addition, it can be extremely difficult to evaluate symptoms in children less than 2 years of age, who are too young to undergo a cardiopulmonary test or other tests requiring collaboration. We identified a cluster of haematological anomalies that, unlike clinical, radiological, or echocardiographic parameters, could be a useful and simple tool for risk stratification in children with cardiac failure. The cut-off limits for haemoglobin, urea, and C-reactive protein were similar to the reported normal values. The prediction score used in our series showed that the survival probability was extremely different in low- and high-risk patients.

The major limitation of our study is its retrospective nature. To avoid bias due to the length of the study, we restricted inclusion criteria to a single disease associated with cardiac failure and limited our analysis to blood test performed in the same centre and available in the majority of patients. We considered only blood tests at first diagnosis, in order to avoid the bias due to the medical treatment. We used multiple statistic tests to strengthen our results. However, our predictor model, to be validated, should be applied to prospective studies.

In conclusion, as in adult patients, cardiac failure due to idiopathic dilated cardiomyopathy in children is accompanied by haematological abnormalities that constitute sensible risk factors of early death or transplantation. Anaemia is highly predictive of early death and should be aggressively treated in order to possibly improve the prognosis of patients at risk. The utilisation of a stratification score might provide a better identification of patients at risk and should allow to optimise medical treatment or offer the possibility of cardiac transplantation to patients with higher risk. In fact, when the diagnosis of dilated cardiomyopathy is made in a child, there is limited time for medical treatment before clinical deterioration or death occurs.

Acknowledgement

We thank Isabelle Szezepanski for her assistance during the collection of data.

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