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Factors affecting mortality in children with dilated cardiomyopathy

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Dilated cardiomyopathy (DCMP) is a heart disease with high mortality rates that is often seen in children. Genetic and infectious reasons are primary in the etiology. The aim of this study was to investigate the etiology of DCMP and the parameters predicting mortality. A retrospective examination was made of 37 patients diagnosed with DCMP between January 2012 and October 2016. Data were recorded from the patient files of age, gender, complaints on presentation, findings of the physical examination, laboratory test results, echocardiography and electrocardiography findings at the time of diagnosis. These parameters were then compared between the surviving and non-surviving patients.

The patients comprised 21 males with a mean age of 27.50±50 months. Diagnosis was made at the age of <12 months in 67.6% patients. Within mean 8 months of diagnosis, 16.2% of the patients were lost to mortality and 83.8% of the patients survived. In 83.3% of the non-surviving patients and in 29% of the surviving patients, sinus tachycardia was present at the time of diagnosis (p=0.023). Corrected QT (QTc) at the time of diagnosis was longer in the non-surviving patients (p=0.007). On ECG, the rate of ST-T wave change was higher in the non-surviving patients (80% vs. 17.8%, p=0.012).

In conclusion, a significant proportion of the patients were diagnosed below the age of one year. In the non-surviving patients, as sinus tachycardia and ischaemic changes on ECG were seen more often and the QTc was longer, these findings could be considered to be predictors of mortality.

Key words: dilated cardiomyopathy, child, myocarditis.

Dilated cardiomyopathy (DCMP) is a type of cardiomyopathy seen primarily as left ventricle dilation but there may also be dilation of both ventricles and heart failure.[1] The incidence of cardiomyopathy has been reported as 4.8/100,000 in infants and 1.3/100,000 in children aged <10 years, and DCMP constitutes approximately 60% of these cases.[2] The leading causes in the etiology are idiopathic, followed by myocarditis, coronary artery disease and other reasons. Familial inheritance is seen in 30-48% of all DCMP patients demonstrating the importance of genetic transfer.[3] The prognosis of the disease is not good. Survival rates have been reported as 63%-90% for 1 year and 20%-80% for 5 years.[4] As the prognosis of DCMP

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patients is not good, patients must be closely monitored after diagnosis and the factors affecting prognosis must be well considered. The aim of this study was to examine patients diagnosed with DCMP and thereby investigate the etiology and factors that could predict mortality.

Material and Methods

The study included a total of 37 patients, aged 7 months-17 years, who were diagnosed with dilated cardiomyopathy (DCMP), were admitted and followed up in the Paediatric Cardiology Department of Dicle University between January 2012 and October 2016. The patient records were examined for data on age, gender, complaints on presentation, consanguineous status of parents, familial history, physical examination findings, laboratory test results, echocardiography (ECHO) and electrocardiography (ECG) findings at the time of diagnosis, results of cardiac catheterisation if applied and the most recent clinical status.

The patients were separated into 2 groups according to the DCMP etiology as those with idiopathic DCMP or other causes. The patients were also separated into 2 groups as survivors and non-survivors and the relationships between these groups and the other parameters were also examined.

Approval for the study was granted by the Etthics Committee of Dicle University (Decision no: 345, dated: 16.12. 2016).

Statistical analyses of the data obtained were made using SPSS vn. 18.0.0 software. Conformity of the data to normal distribution was assessed using the Shapiro-Wilks test. In the comparison between 2 groups of continuous variables with normal distribution, the Independent Student's t-test was used and the Mann Whitney U-test was applied for groups not showing a normal distribution. To determine relationships between variables, Pearson Correlation analysis was applied. The Pearon Chi-square test and Fisher's Exact test were used for categorical variables. Measurable parameters were reported as mean±standard deviation (SD) and categorical variables as number (n) and percentage (%). A value of $p<0.05$ was accepted as statistically significant.

Results

The patients comprised 21 (56%) males and 16 (44%) females with a mean age of 27.50±50 months (7 months–17 years). Body weight at the time of diagnosis was 10.6± 10.9 kg. There was parental consanguinity in 17 (46%) patients and a familial history of DCMP in 4 (10.8%) patients. Diagnosis was made at the age of <12 months in 25 (67.6%) patients, at 13 months- 5 years in 7 (18.9%), and >5 years in 5 (13.5%).

In the month before diagnosis, a history of upper respiratory tract infection (URTI) was determined in 27 (73%) patients, acute gastroenteritis (AGE) in 6 (16%) and both URTI and AGE in 4 (11%). The complaints on presentation and physical examination findings at the time of diagnosis are shown in Table I.

In 10 patients, viral etiological evaluation could not be performed and in 21 (56.8%) patients, no etiology could be determined. Cytomegalovirus was determined in three patients, rubella in one and influenza A (H1N1) in one. In six patients, there was bacteriological production in either one of the blood and pleural fluid cultures. These patients were evaluated with DCMP secondary to myocarditis associated with infectious reasons. The etiologies of the patients are shown in Table II. The laboratory test results of the patients on first presentation are shown in Table III.

In the transthoracic ECHO examinations, mean left ventricle end-diastole diameter (LVEDd) was determined as 41.57±10.95 mm, mean left ventricle end-systole diameter (LVESd) as 32.4±10 mm, and mean left ventricular fractional shortening (LVFS) as 19.5±5%. At the time of diagnosis, mean left ventricle ejection fraction (LVEF) was determined as 38.9±9.2% (range, 20-56%) and at the end of 1-59 months follow-up (median 27 months), the final mean LVEF value was 58.1±12.9% (range, 28-76%). In 20 (54%) patients, normal LVEF levels (range, 56-78%) were obtained.

Table I. Complaints on Presentation and Physical Examination Findings at the Time of Diagnosis.

	Number	%
Complaints on presentation*		
No complaint	3	8
Shortness of breath	17	46
Cough	17	46
Fever	13	35
Not suckling	6	16
Vomiting	5	13
Sweating	2	5
Bruising	3	8
Palpitations	3	8
Other complaints**	12	32
Physical examination findings*		
Cardiac murmur	26	70
Pulmonary rales	15	40
Tachycardia	14	38
Tachypnea	14	38
Hepatomegaly	5	14
Reduced pulmonary sounds	4	11
Oedema	2	5
Other physical examination findings***	8	22

*There were patients with more than one complaint and physical examination finding
** Diarrhea, listlessness, wheezing, chest pain, headache
*** Hyperemia in the oropharynx, hypertension, splenomegaly, retarded neuromotor development

Table II. The Etiology of The Cardiomyopathy.

Etiology	Number	%
Idiopathic	21	56.8
Infectious myocarditis	9	24.3
Cytomegalovirus	*3*	*30*
Rubella	*1*	*10*
Influenza A (H1N1)	*1*	*10*
Bacterial agent	*4*	*44*
Chronic renal failure	3	8.1
Metabolic disease (fatty acid oxidation defect)	1	2.7
Doxorubicin	1	2.7
Aortic coarctation	1	2.7
ALCAPA	1	2.7
Total	37	100

ALCAPA: Anomalous Left Coronary Artery From the Pulmonary Artery

Table III. Laboratory Test Results of The Patients on First Presentation.

Laboratory test	Result*
Hemoglobin (gr/dl)	10.4 ± 1.5
Leukocytes (mm^3)	12051 ± 4757
Thrombocytes (mg/dl)	361135±132000
Urea (mg/ld)	29.54 ± 31.15
Creatinine (mg/dl)	0.59 ± 0.56
Uric acid (mg/dl)	5.6 ± 2.9
Sodium (mg/dl)	136.6 ± 3.5
Calcium (mg/dl)	9.2 ± 0.95
Glucose (mg/dl)	90.3 ± 17.5
ALT (IU)	95.1 ± 285
AST (IU)	192.2 ± 597.3
CK (mg/dl)	390 ± 844.5
LDH (mg/dl)	636 ± 1060
Troponin (ng/ml)	0.56 ± 1.32
CK-MB (ng/ml)	13.3 ± 17.2
Albumin (mg/dl)	3.5 ± 0.47
CRP (mg/dl)	1.1 ± 2.36
Erythrocyte Sedimentation rate (mm/hour)	8.55 ± 7.33

* Mean ± standard deviation
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatinine kinase; CK-MB: Creatinine kinase-MB; CRP: C-reactive protein; LDH: Lactate dehydrogenase

Mortality was seen in 6 (16.2%) patients at 2-33 months (median 8 months) after diagnosis, and 31 (83.8%) survived. Mortality was seen in three patients aged <12 months and in three patients aged 5 years or older. The mortality rate of those aged ≥5 years was statistically significantly higher than that of those aged <12 months ($p<0.05$). In 4 (67%) of the 6 patients with mortality, death was determined to have occurred within one year of diagnosis.

The cases were separated into 2 groups as non-survivors (Group I) and survivors (Group II) and characteristics were compared between the groups. In Group I, 3 (50%) patients were diagnosed at the age of <12 months and 3 (50%) at the age of ≥ 5 years; there were no patients in the 1-5 years age group. In Group II, diagnosis was made at the age of <12 months in 22 (71%) patients, at 13 months-5 years in 7 (23%) and >5 years in 2 (6%).

The complaints on presentation and the physical examination findings of Groups I and II were compared. No statistically significant difference was determined between the groups in respect to complaints on presentation. In the evaluation of the physical examination findings, sinus tachycardia confirmed with ECG was present at the time of diagnosis in 5 (5/6; 83.3%) and heart rate was within the normal limits for age in 1 (16.7%) of the non-surviving patients. Sinus tachycardia was determined in 9 (29%) and heart rate within the normal limits for age in 22 (71%) of the surviving patients. Of the 14 patients determined with sinus tachycardia at the time of diagnosis, 9 (64.3%) survived and 5 (35.7%) did not survive and of the 23 patients not determined with sinus tachycardia at the time of diagnosis, 22 (95.7%) survived and 1 (4.3%) did not survive. Sinus tachycardia at the time of diagnosis was determined at a statistically significantly higher rate in Group I ($p=0.021$). No statistically significant difference was determined between the groups in respect to other physical examination findings. The complaints on presentation and the physical examination findings of Groups I and II are shown in Table IV.

The 12-lead surface ECG findings were compared between the two groups. The corrected QT (QTc) according to the Bazzet formula was determined as median 0.40 secs (range, 0.39-0.41secs) in Group 1 and median 0.38 secs (range, 0.26-0.41 secs) in Group II and the difference between the groups was statistically significant ($p=0.007$). Pathological Q wave, ST segment and T-wave changes that suggest ischaemia were determined as statistically significantly greater in Group I than in Group II ($p=0.013$). The ECG findings of both groups are shown in Tables V and VI. As the ECG records of 4 patients could not be accessed, the ECG data of 33 patients were examined.

The age of the patients, certain cardiac markers, ECHO and other ECG findings are shown in VI. In the evaluation of the ECHO findings, mean LVESd was determined as

Table IV. Complaints on Presentation and Physical Examination Findings of Group I and Group II.

Complaint *	Group I (n:6)		Group II (n:31)		P Value
	n	%	n	%	
Shortness of breath	2	33.3	15	48.4	0.667
Cough	0	0	2	6.5	1.000
Fever	2	33.3	3	9.7	0.177
Not suckling	0	0	3	9.7	1.000
Vomiting	1	16.6	2	6.5	0.421
Sweating	1	16.6	5	16.1	1.000
Bruising	2	33.3	13	42	1.000
Palpitations	4	66.7	13	42	0.383
Other complaints**	3	50	9	29	0.728
Physical examination*					
Murmur	5	83.3	21	67.7	0.646
Rales	3	50	12	38.7	0.670
Tachycardia	5	83.3	9	29	0.021
Tachypnea	2	33.3	12	38.7	1.000
Hepatomegaly	1	16.7	4	12.9	1.000
Oedema	1	16.7	1	3.2	0.302
Other ***	3	50	5	16.1	0.510

*There were patients with more than one complaint and physical examination finding
** Diarrhea, listlessness, wheezing, chest pain, headache
*** Hyperemia in the oropharynx, hypertension, splenomegaly, retarded neuromotor development

Table V. 12-Derivation Surface ECG Findings of Group I and Group II.

ECG finding	Group I		Group II		P Value
	n	%	n	%	
Ventricular hypertrophy	n	%	n	%	
Left ventricle	3	60	6	21.4	0.186
Left and right ventricle	0	0	3	10.8	
No hypertrophy determined	2	40	19	67.8	
Total	5	100	28	100	
Findings of ischaemia					
Present	4	80	5	17.8	0.013
Absent	1	20	23	82.2	
Total	5	100	28	100	

40.5±16.8 mm in Group I and 30.9±7.6 mm in Group II and the difference between the groups was statistically significant (p=0.029). The mean LVEF values were lower in Group I than in Group II, but the difference between the groups was not statistically significant (p=0.071).

Discussion

The leading causes of DCMP have been reported as idiopathic reasons followed by myocarditis.[5] De Boer et al.[6] reported that DCMP was secondary to myocarditis in 14-22% of their patients and the majority were idiopathic. Similar to findings in literature,

Table VI. Certain cardiac markers, ECHO and 12-Lead ECG Findings of Group I and Group II.

Parameters	Group 1	Group 2	P value
Age (months)*	5 (1.3-72)	7 (0.5-204)	0.433
Troponin (ng/ml)*	0.085 (0.04-0.13)	0.9 (0.01-0.92)	0.751
CK-MB (ng/ml)*	25.4 (4.26-46.5)	7.18 (0.72-54.33)	0.356
Electrocardiography			
QTc (ms)*	0.40 (0.39-0.41)	0.38 (0.26-0.41)	0.007
Echocardiography			
LVEDd (mm)	48.8 ± 20.7	40.1 ± 7.7	0.076
LVESd (mm)	40.5 ± 16.8	30.9 ± 7.6	0.029
LVSF (%)	17.5 ± 5.7	19.9 ±4.9	0.288
LVEF (%)	31.8 ± 8.9	40.3 ±8.7	0.071

Data are presented as mean±SD
*median (range)
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatinine kinase; CK-MB: Creatinine kinase-MB; CRP: C-reactive protein; LVEF: left ventricle ejection fraction; LVSF: Left ventricle shortening fraction; LDH: Lactate dehydrogenase; LVEDd: left ventricle end diastole diameter; LVESd: left ventricle end systole diameter, QTc: corrected QT distance

the etiology could not be determined in 21 (56.8%) of the current study patients. Of those where etiology was determined, myocarditis was similarly determined in a significant proportion. In a previous study, when endomyocardial biopsy was performed on patients diagnosed with DCMP, the disease was determined to be secondary to myocarditis in the majority of patients thought to be idiopathic.[7] As serological studies for causes of primary viral myocarditis (coxsackie virus, adenovirus, parvovirus B19) could not be performed in our hospital at the time of the study, it can be considered that the rate of viral myocarditis could have been higher and idiopathic reasons could have been lower.

In the current study, 27 (73%) had URTI history within the previous month, 6 (16%) patients had a history of AGE and 4 (11%) had a history of both URTI and AGE. Although the rate of DCMP associated with myocarditis was found to be 24.3%, the high rate of 73% of URTI history suggests that the rate of viral etiology could be higher than that determined in the study.

Various symptoms may develop in DCMP patients. Symptoms are generally related to insufficient perfusion and congestion. Respiratory system symptoms are frequent and listlessness, chest and abdominal pain, nausea and vomiting and delayed development are also frequently seen symptoms.[8] In the current study, only 3 (8%) patients had no complaints on first presentation, and in other patients the most common complaints were shortness of breath, cough and fever. In the physical examination evaluation of the current study, cardiac murmur, pulmonary rales, tachycardia, tachypnea, hepatomegaly, reduced pulmonary sounds and oedema were determined. These findings are expected in DCMP patients and develop as a result of pulmonary and systemic venous congestion.

The ECG examinations of patients diagnosed with DCMP are generally pathological. Left ventricle hypertrophy, ST-segment and T-wave changes are often observed and advanced anomalies, low voltage and pathological Q wave may also be seen.[8] A previous study showed ST-T changes in 50% of cases, left ventricle hypertrophy in 45%-70% and sinus tachycardia in several patients.[1] In the ECG examinations of the current study, ventricular hypertrophy was observed in 88% of patients and findings of ischaemic changes in 64.9%. In patients describing symptoms compatible with these ECG anomalies that are seen in the majority of patients, the ECG findings of ventricular hypertrophy and ischaemic changes should be a warning in respect to DCMP diagnosis.

The 5-year survival rate has been reported as 50% in DCMP.[9] Friedman et al.[10] determined a mortality rate of 16% in children diagnosed with DCMP. In the current study, the mortality rate was determined as 16.2%, similar to the rates in literature.

Of the 6 patients with mortality in the current study, 4 (67%) died within one year of diagnosis. Survival of more than one year was seen in 90% of the patients. There are different data in the literature related to mortality according to age groups. While some authors have reported higher mortality rates before the age of the first year[11,12], Burch et al.[13] reported that mortality was higher in those over the age of 2 years. When mortality was examined according to age groups in the current study, the rate of non-survivors aged ≥5 years was observed to be greater than that of survivors.

The mortality rate of patients with sinus tachycardia at the time of diagnosis was determined to be statistically significantly higher than the mortality rate of all the patients. A point requiring attention in DCMP is whether tachycardia has caused cardiomyopathy or whether tachycardia is caused by cardiomyopathy.[14] In the current study, there was no supraventricular or ventricular tachycardia, but sinus tachycardia was present. This therefore suggested that sinus tachycardia had developed as a result of DCMP. Findings of ischaemia on ECG were determined at a statistically significantly higher rate in non-survivors than in survivors. A previous study reported that the prognosis and outcomes of ischaemic or irreversible cardiomyopathies were worse than in non-ischaemic cardiomyopathy.Q In addition, the QTc values of the non-surviving patient group in the current study were determined as higher than those of the surviving patients. Previous studies have reported that the QTc value was increased in DCMP patients and this increase was a marker of poor prognosis in patients at different degrees.[16,17]

In conclusion, while a significant proportion of the patients diagnosed with DCMP were aged 12 months and younger, mortality was determined at a higher rate in those diagnosed at age 5 years and over. No significant difference was determined between survivors and non-survivors in respect of complaints on presentation, physical examination findings and laboratory test values, whereas the presence of sinus tachycardia, findings of ischaemia and prolonged QTc on ECG were parameters predicting mortality. Therefore, it must be emphasised that there should be close monitoring of children diagnosed with DCMP in respect to ECG findings.

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