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Original article

Left ventricular reverse remodeling with infantile dilated cardiomyopathy and pitfalls of carvedilol therapy

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ABSTRACT

Background: The left ventricular reverse remodeling (LVRR) in idiopathic dilated cardiomyopathy (DCM) and the treatment with carvedilol in infants with severe heart failure remain poorly understood.
Methods: We reviewed the medical records of 5 infants around 12 months old referred to our hospital with severe heart failure due to DCM. Increased left ventricular fractional shortening (LVFS) by more than 10% and the percent of normal of left ventricular end-diastolic dimension (%LVDd) less than 120% were defined as LVRR in this study.
Results: DCM onset ranged from 8 to 16 months. Initial treatment of their acute heart failure was successful in all 5 but 4 patients relapsed despite the usual dose of carvedilol (induction 0.02–maintenance 0.4 mg/kg/day), and developed worsening heart failure. Brain natriuretic peptide (BNP) levels which increased again after the acute treatment had fallen subsequent to discontinuing or decreasing carvedilol. Over 24 months, LVFS had increased from $11 \pm 2\%$ (mean $\pm$ SD) to $34 \pm 5\%$ ($p < 0.05$), and %LVDd decreased from $149 \pm 27\%$ to $108 \pm 11\%$ ($p < 0.05$).
Conclusions: LVRR was found at 2 years after the onset of DCM. Usual dose induction of carvedilol therapy can sometimes worsen heart failure after successful initial conventional treatment for the acute heart failure in DCM. Close control of carvedilol treatment may determine the prognosis of infantile DCM around 12 months old. It is prudent to increase low-dose carvedilol slowly corresponding with the BNP level.

Introduction

The prognosis in individual children with idiopathic dilated cardiomyopathy (DCM) is unpredictable ranging from death to intractable heart failure to occasional spontaneous recovery [1,2]. Unfortunately, there is no marker for the prognosis of DCM. Everitt et al. reported a series of children of whom 22% recovered normal left ventricular function and size; 51% had died or undergone heart transplantation, and 27% had persistently abnormal echocardiograms 2 years post acute onset [3]. They reported that younger age and lower left ventricular end-diastolic dimensions were the best indicators for improvement. Griffin et al. documented that the prognosis in DCM <2 years of age at onset was better than at onset >2 years [4]. The cause and prognosis of DCM are diverse, and its characteristics appear to differ depending on the age at the onset. On the other hand, anti-heart failure therapies with established efficacy in adults appear to have a limited impact on pediatric outcomes [5–9]. We report the clinical course and the pitfalls of carvedilol treatment in patients who presented with infantile DCM around 12 months of age.

Methods

We retrospectively reviewed the clinical course and left ventricular reverse remodeling (LVRR) from the medical records of five infants aged around 12 months referred to our hospital between 2006 and 2013 with DCM. There were three boys and two girls. The onset of DCM ranged from 8 to 16 months, median 13 months. In this study, the time of the initial admission was regarded as the onset of DCM. The left ventricular end-diastolic dimension (LVDd) and the left ventricular fractional shortening (LVFS) in two-dimensional echocardiograms (2-DE) during the clinical course were analyzed. The changes in brain natriuretic peptide (BNP) levels were also tabulated in all five patients. LVDd

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was also calculated as % of normal for body surface area (Normal LVDd = log BSA × 31.4 + 40.2). Furthermore, we documented changes in mitral regurgitation (MR) in 2-DE and T waves in V_6 in 12-lead electrocardiogram. An increase of LVFS more than 10% and %LVDd less than 120% were defined as LVRR for this study. We investigated LVFS and %LVDd in the 4 points based on the time after the onset. The timing of the 4 points was (1) onset, (2) 6 months, (3) 12 months, and (4) 24 months.

The mean values are shown as mean ± 1 standard deviation. After repeated measure ANOVA was performed, Tukey's honesty significant difference test was used for differences between groups. Differences were considered statistically significant at $p < 0.05$.

Results

Outline of clinical course and the treatment of heart failure

The presentation at the onset of DCM was as follows. Gastrointestinal symptoms including vomiting and diarrhea were the most frequent and occurred in 3 patients (patients 2, 4, 5). Poor feeding and failure to thrive for a few months before the onset occurred in 3 patients (patients 3, 4, 5). Dyspnea and cardiogenic shock occurred in 2 patients (patients 1, 4). Chest X-ray showed cardiomegaly in all five. Mean cardiothoracic ratio in the chest X-ray was 62% in 5 patients, and a low LVFS (mean ± SD, 11 ± 2%) and a dilated LVDd 41.0 ± 7.1 (149 ± 27% of normal) were detected by 2DE. The degree of MR in 2-DE were as follows: moderate 2 patients (patients 1, 3) and slight 3 patients (patients 2, 4, 5). Creatine phosphokinase was not elevated. All patients had been diagnosed as having DCM. No perfusion defects were found in ^{99m}Tc myocardial perfusion imaging in any patient. Negative T waves in V_6 in the 12-lead electrocardiograms were present in two patients (patients 1, 5) and flat T waves were seen in three patients (patients 2, 3, 4).

All five patients, responded to conventional therapy for acute heart failure using catecholamines and phosphodiesterase (PDE) III inhibitor. Oral medicines given after treating acute heart failure were as follows. Digoxin, 0.01 mg/kg/day, furosemide and spironolactone, 3–4 mg/kg/day, and enalapril, 0.1–0.2 mg/kg were administered at some stage in all five patients (Table 1). All five patients had carvedilol therapy. Four patients experienced worsening heart failure after the administration of carvedilol. Four patients (the exception being patient 1) were referred to our hospital as heart transplantation candidates, because of intractable heart failure. The carvedilol was stopped in one patient (patient 2), decreased in one patient (patient 3), and decreased and discontinued in two patients (patients 4, 5). The re-induction dose of carvedilol was 0.02 mg/kg/day in the 3 patients, started when BNP had decreased to less than 400 pg/ml. The maintenance dose of carvedilol was 0.05 mg-0.20 mg/kg/day 1 year after the onset of DCM. Mean cardiothoracic ratio in the chest X-ray was 52% in five patients, and mean LVFS and mean %LVDd measured by 2-DE were 26 ± 12% and 121 ± 16% of normal, respectively. Twenty-four months after the onset of DCM, mean LVFS and mean %LVDd detected by 2-DE were 34 ± 5% and 108 ± 11% of normal. MR had improved for 2 years in four patients. Slight MR was present only in patient 3. T waves in V_6 in the 12-lead electrocardiograms were positive in four patients the exception was patient 4. New York Heart Association class was I in all five patients.

Brief histories

Patient 1

A nine-month old boy was referred to our hospital because of pallor and dyspnea after bathing. He had undergone mechanical respiratory ventilation under deep sedation for 3 months (Fig. 1). Four months after the onset of DCM, enalapril and digoxin were administered, and subsequently carvedilol (0.003 mg/kg/day) was started 8 months after the onset. His LVFS increased 10 months after the onset of DCM. Thirty-seven months after the onset of DCM his indices were improved to 96% of normal and 39%, respectively. A ZASP (a Z-band alternatively spliced PDZ motif-containing protein) mutation was detected. He had developmental delay because of neurological disease.

Patient 2

A 16-month-old girl developed pallor and vomiting. Acute heart failure initially improved with catecholamine and PDE III inhibitor but subsequently worsened and her BNP increased dramatically, after discontinuing positive inotropic agents and starting carvedilol (0.025 mg/kg/day) at 16 days (Fig. 2). Subsequently she

Table 1
Treatment in acute and late period.

Patient	1	2	3	4	5
Gender	Male	Female	Male	Female	Male
Age at onset (months)	9	16	8	13	15
Acute treatment					
Duration					
MRS (days)	99			50	
DOA (days)	191	116	7		
DOB (days)	222	169	7	359	1
PDE III inhibitor (days)	287	193	10	387	19
Others	hANP	Furosemide	Furosemide	hANP	Furosemide
	Furosemide			Furosemide	
				ECMO, CHDF	
Late period					
Oral medication (mg/kg)					
Digoxin	0.01 → off	0.01	0.01	0.01	0.01
Furosemide	3 → off	3 → off	4.5 → off	3 → 2	4
Spironolactone	3 → off	3 → off	3.4 → off	3 → 2	4
Trichlormethiazide					0.01 → 0.005
Pimobendan	0.005 → off	0.01 → off		0.01	0.01
Enalapril	0.1 → off	0.1	0.2	0.1	0.2
Carvedilol (max) mg/kg	0.1	0.14	0.35	0.47	0.15
Carvedilol (maintenance)	0.05	0.05	0.2	0.09	0.06

MRS, mechanical respiratory support; DOA, dopamine; DOB, dobutamine; PDE III inhibitor, phosphodiesterase III inhibitor; hANP, human atrial natriuretic peptide; ECMO, extracorporeal membrane oxygenation; CHDF, continuous hemodialysis filtration.