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Original article

Improvement of the outcome in patients with infantile dilated cardiomyopathy over three decades – The usefulness of long-term gradually medical supportive care

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ABSTRACT

Background: The treatment of heart failure has changed with the use of angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers since the middle of the 1990s. However, the outcome in infantile dilated cardiomyopathy (DCM) when treated with them remains poorly understood.
Methods: We reviewed the medical records of infants with DCM within 24 months old in our hospital between 1979 and 2012, and compared the outcome in the later group (1997–2012) with that in the early group (1979–1996). The survival and cardiac event (CE)-free survival rates were calculated by the Kaplan–Meier method.
Results: There were 20 patients in the early group and 24 patients in the later group. The median left ventricular fractional shortening at the onset of disease in the early and later groups were 11% (range 4–17%) and 12% (range 4–25%), respectively. In the later group, ACEIs and beta-blockers were administered in 22 and 21 patients, respectively. An usual low-dose induction of carvedilol therapy (0.01–0.02 mg/kg/day) sometimes worsened the heart failure in 9 patients (43%) after the successful initial conventional treatment for acute heart failure. Nineteen patients died and 25 survived. The CEs were as follows: heart transplantation 4, mitral valvuloplasty 1, Batista operation with mitral valve replacement 1, and cardiac resynchronization therapy in the late period 1. The 20-year survival rate in the early and later groups were 5% (95% CI 0.7–28) and 100%, respectively ($p < 0.001$). The 2-year CE-free survival rate in the early and later groups were 5% (95% CI 0.7–28) and 83% (95% CI 59–91), respectively ($p < 0.001$).
Conclusions: The outcome in patients with infantile DCM has significantly improved with careful acute and chronic treatments using ACEIs and beta-blockers since the 2000s. Adopting a long-term supportive treatment during a period of low ventricular function and the use of beta-blockers corresponding to each patient's condition were key to survival.

Introduction

The prognosis in infantile dilated cardiomyopathy (DCM) is unpredictable, and ranges from death to almost normal recovery [1,2]. Since the introduction of angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers, the outcome in patients with severe heart failure has remarkably improved in adults [3–5]. The Organ Transplant Law in Japan was revised and enforced in 2010, which allowed for pediatric heart transplantations. Further, a pediatric left ventricular assist device (EXCOR, Berlin Heart, Inc., Berlin, Germany) became possible from 2015 [6]. However, the number of patients who can undergo a heart transplantation is limited in Japan. Therefore, the medical therapy for severe heart failure is important to avoid a heart transplantation. The use of ACEIs and beta-blockers appears to have some impact on the pediatric outcomes [7–9]. We reviewed the outcome in infants with DCM within 24 months over the three decades before treatment by devices in our institution.

Methods

We retrospectively reviewed the clinical course and outcome from the medical records of 46 infants with DCM aged younger

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than 24 months old in our hospital between January 1979 and August 2012. Two patients with tachycardia-induced DCM were excluded from this study. At presentation, the creatine phosphokinase level was not elevated in any of the 44 patients. There were 17 boys and 27 girls. The onset of DCM ranged from 0 to 23 months, with a median of 5 months. The follow-up period ranged from 48 days to 36 years, with a median of 7 years. Nine patients in the later group were referred to our hospital as heart transplantation candidates, because of intractable heart failure. In our hospital, ACEIs and beta-blockers for the treatment of heart failure have been used since the middle of 1990s.

Therefore, we compared the survival rate and cardiac event (CE)-free survival rate between the two groups based on the time of presentation. The early group ranged from 1979 to 1996, and the later group was from 1997 to 2012. The CEs in this study included heart transplantation, mitral valve replacement, mitral valvuloplasty, and cardiac resynchronization therapy (CRT). We reviewed how the medicine was used for heart failure in each patient. Further, we analyzed whether the use of ACEIs and beta-blockers have had an influence on survival.

The presentation at the time of the onset of DCM, cardiothoracic ratio (CTR) in the chest X-ray, left ventricular end-diastolic dimension (LVDd), and left ventricular fractional shortening (LVFS) in the two-dimensional echocardiogram (2DE) during the clinical course were analyzed. The values of the brain natriuretic peptide (BNP) levels, LVDd, and LVFS at 5 years after the onset of DCM were also investigated in the later group. The LVDd was also calculated as the % of a normal body surface area (normal LVDd = logBSA $\times$ 31.4 + 40.2) [10].

Statistical analysis

The values of the parameters are shown as median and its range. The unpaired t-test was used to compare the differences between the groups. The survival rate and CE-free survival rate were calculated by the Kaplan–Meier method with the 95% confidence interval (CI). Differences were assessed by the log-rank test. We assessed the medicine affecting the outcome in the patients with DCM by a multivariate analysis using the Cox proportional hazards model. Differences were considered statistically significant at a $p < 0.05$. JMP 9.0 software (SAS Institute, Cary, NC, USA) was used as the statistical software.

Results

Presentation at the onset of DCM

The presentation at the time of the onset of DCM was as follows (Table 1). Respiratory distress including cyanosis, dyspnea, and tachypnea were frequently detected in 22 patients. Gastrointestinal symptoms including vomiting and diarrhea were observed in 4 patients. Poor feeding and failure to thrive for a few months before the onset of the disease occurred in 7 patients. Cardiomegaly detected during a common cold was observed in 4 patients, and cardiac dysfunction by fetal echocardiography 1. Heart murmurs and the familial history of cardiomyopathy were observed in 5 and 1 patient, respectively. Seven patients (16%) had a familial history of cardiac disease, and 6 of those 7 patients had DCM.

In the later group, 4 among 7 patients had the abnormality of genetic testing. Three patients, had a beta-myosin heavy chain 7 mutation (MYH7). A Z-band alternatively spliced PDZ motif-containing protein (ZASP) mutation was detected. He had a developmental delay due to neurological disease. The other patient was diagnosed with mitochondrial cardiomyopathy. One patient had dyssynchrony due to complete left bundle branch block (CLBBB) and another Wolff-Parkinson-White syndrome on the 12-lead electrocardiogram. Two patients underwent a coil embolization for a small patent ductus arteriosus. Further, two patients had autism.

Table 1
Characteristics and treatment in patients with infantile DCM.

Group Year		Early group 1979–1996		Later group 1997–2012
Number of patients		20		24
Male/female		8/12		9/15
Age at the diagnosis (months)		6 (0–23)		5 (1–16)
Main symptom and sign at the detection				
Respiratory distress		8		14
Gastrointestinal problem		3		1
Poor body weight gain		2		5
Cardiomegaly		4		0
Heart murmur		2		3
Others		1		1
Parameters at the initial presentation	*n*	Median (range)	*n*	Median (range)
CTR (%)	17	70 (57–73)	24	65 (54–73)
LVDd (% of normal)	17	165 (129–210)	24	163 (123–250)
LVFS (%)	17	11 (4–17)	24	12 (4–25)
Supportive treatment				
Mechanical ventricular assist		1		5
Catecholamines		8		10
PDEIII inhibitor		0		17
Medicine				
Digoxin		20		13
Furosemide		20		23
Supilonolactone		18		23
Enalapril		0		22
Valsaltan		0		3
Carvedilol		1		19
Metoprolol		0		2
Pimobendane		0		3
NYHA class at the latest time				
I		0		23
II		1		0
Unknown		0		1

DCM, dilated cardiomyopathy; NYHA, New York Heart Association; CTR, cardiothoracic ratio; LVDd, left ventricular end-diastolic dimension; LVFS, left ventricular fractioning shortening; PDE, phosphodiesterase.

The median age at the detected time of DCM in the early group was 6 months (range 0–23, $n = 20$), and that in the later group was 5 months (range 1–16, $n = 24$) (Table 1). There were no significant differences between the two groups. The median CTR in the chest X-ray at the time of the initial presentation was 70% (range 57–73, $n = 17$) in the early group and 65% (54–73, $n = 24$) in the later group. The median LVDd and median LVFS by 2DE in the early group were 165% (range 129–210, $n = 17$) and 11% (range 4–17, $n = 17$), respectively. In the later group, they were 163% (range 123–250, $n = 24$) and 12% (range 4–25, $n = 24$), respectively. There were no significant differences in those parameters between the two groups. The value of the BNP at the time of the initial presentation ranged from 6.1 to 7535 pg/ml, with a median of 1309 pg/ml.

Treatment in the early and later groups

In the early group, catecholamines were administered in 5 patients, and vasodilators in 2 patients. Furosemide was administered intravenously in the acute phase in all 20 patients (digoxin, 0.01 mg/kg/day, and furosemide and spironolactone, 3 mg/kg/day). In the later group, 18 patients, responded to conventional therapy for acute heart failure using catecholamines or phosphodiesterase (PDE) III inhibitors. The time of low-dose cathecholamine ranged from 7 days to 359 days with a median of

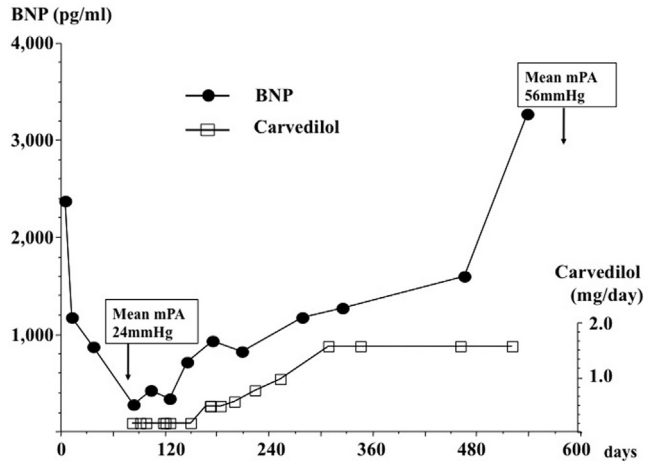

Fig. 1. Changes in the BNP level with the dose of carvedilol. She was diagnosed with dilated cardiomyopathy at 2 months of age. Her acute heart failure initially improved with catecholamines and phosphodiesterase III inhibitors. However, subsequently her condition worsened and her BNP level increased after increasing the carvedilol. She underwent a heart transplantation at 23 months old outside Japan. BNP, brain natriuretic peptide; mPA, main pulmonary artery.

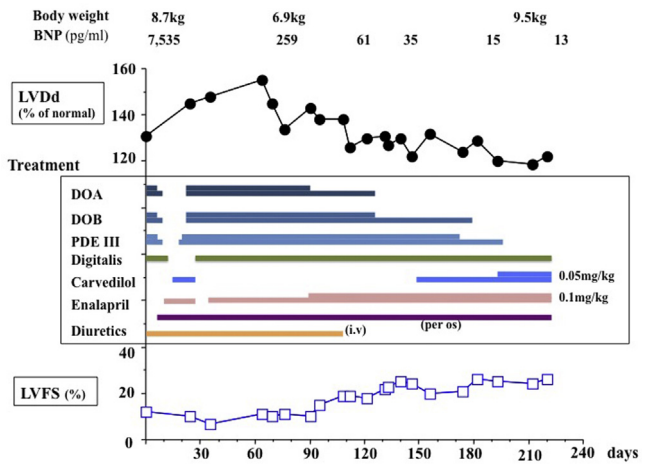

Fig. 3. Changes in the left ventricular parameters in the two-dimensional echocardiograms with treatment in the patient shown in Fig. 2. After her condition worsened, DOA, DOB, and PDE III inhibitor were re-started. Further, digoxin and enalapril were started. She was referred to our hospital for a heart transplantation. DOA, DOB, and PDE III inhibitor were stopped at 116 days, 169 days, and 193 days, respectively. Her LVFS increased 4 months after the onset of dilated cardiomyopathy (DCM). Carvedilol at 0.02 mg/kg/day was re-started 5 months after the onset. Her LVDd and LVFS with carvedilol 0.05 mg/kg/day, 24 months after the onset of DCM improved to 107% of normal and 37%, respectively. BNP, brain natriuretic peptide; LVFS, left ventricular fractional shortening; % LVDd, percent of normal left ventricular end-diastolic dimension; DOA, dopamine; DOB, dobtamine; PDE III, phosphodiesterase III inhibitor.

169 days. The oral medications given after treating acute heart failure were as follows: digoxin, 0.01 mg/kg/day, furosemide and spironolactone, 3 mg/kg/day, and enalapril, 0.1 mg/kg (Table 1). Diuretics were administered in 23 patients. Twenty-two patients had taken enalapril and three valsartan. In the beta-blocker therapy, 19 patients received carvedilol and 2 metoprolol. Nine patients experienced worsening heart failure after the administration of carvedilol. All 9 patients were administered with carvedilol, when the BNP level became more than 300 pg/ml immediately after an acute heart failure episode (Figs. 1 and 2). The carvedilol was stopped in 5 patients, and the dosage was decreased in one. Three patients who continued on beta-blockers with the same dose underwent a heart transplantation outside Japan. The 5 patients who stopped or decreased the carvedilol survived and their LVFS improved with the very low dose re-induction therapy in the late period (Fig. 3). The re-induction dose of carvedilol was 0.002 mg/kg/day in 3 patients, and was started when the BNP level had decreased to less than 200 pg/ml. The dose of carvedilol was increased carefully and gradually with the BNP guiding. The maintenance dose of carvedilol was 0.05–0.40 mg/kg/day.

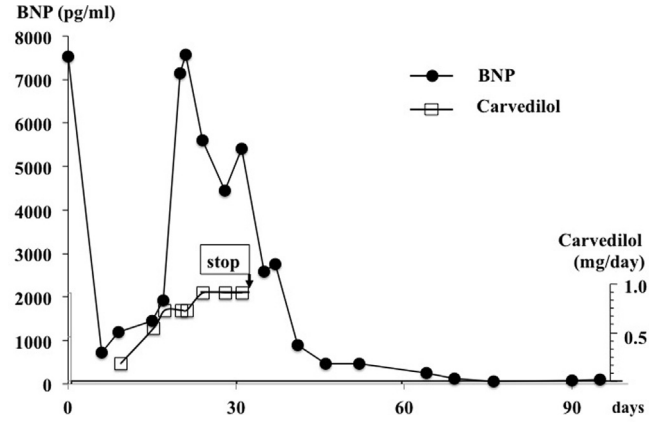

Fig. 2. Changes in the BNP level with the dose of carvedilol. A 16-month-old girl developed pallor and vomiting. Her acute heart failure initially improved with catecholamines and phosphodiesterase III inhibitors, but subsequently worsened and her BNP level increased dramatically after discontinuing positive inotropic agents and starting carvedilol (0.025 mg/kg/day) at 16 days. Carvedilol was increased to 0.14 mg/kg/day for two weeks. Her general condition worsened. The BNP level decreased after discontinuing the carvedilol. BNP, brain natriuretic peptide.

Cardiac events and outcome

In the early group, 19 (95%) out of 20 patients died and 1 survived (Fig. 4). The interval from the onset of DCM to death ranged from 48 days to 19 months, with a median of 10 months. The cause of death was as follows: heart failure 16 patients, sudden death 2, and pneumonia 1. One patient that survived underwent a Batista surgery with mitral valve replacement at 17 years old for severe heart failure and repeated episodes of atrial flutter. On the other hand, all 24 patients survived in the later group. The CEs were as follows: heart transplantation in 4 patients, mitral valvuloplasty in 1, and cardiac resynchronization therapy (CRT) in 1. Four patients underwent heart

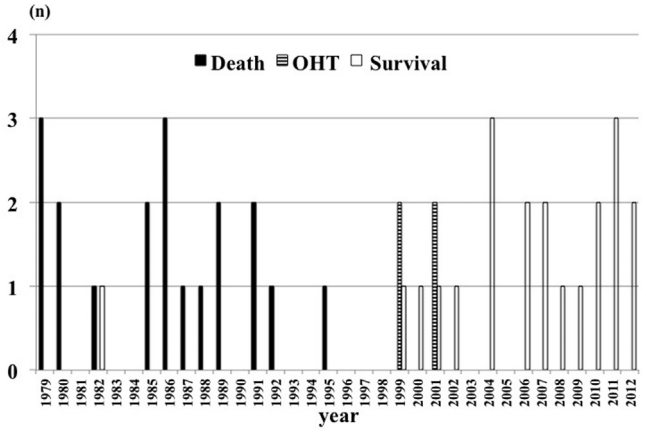

Fig. 4. Outcome in patients with dilated cardiomyopathy based on the year. OHT, orthtropic heart transplantation.

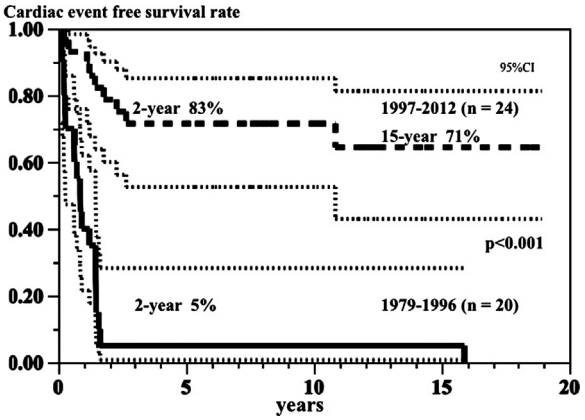

Fig. 5. Cardiac event-free survival rate after the onset of dilated cardiomyopathy in each group. CI, confidence interval.

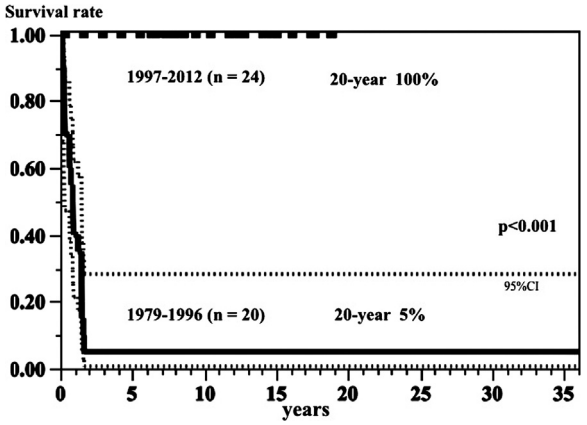

Fig. 6. Survival rate after the onset of dilated cardiomyopathy in each group. CI, confidence interval.

transplantation outside Japan within 2 years after the onset of DCM. Three among the four patients had severe complications excluding cardiac disease after their heart transplantation. Two patients underwent chemotherapy for post-transplant lymphoproliferative disease within 2 years after the heart transplantation. One patient with heart transplantation had a renal transplantation at 14 years old, because of renal failure due to tacrolimus. A 15-month-old girl with a MYH7 mutation underwent mitral valvuloplasty after 3 months for severe mitral regurgitation. Another patient with CLBBB underwent CRT at 11 years old. He had intractable heart failure at the onset of DCM. First, digoxin was administered intravenously under deep sedation with mechanical respiratory support, and intravenous and continuous very low-dose propranolol at 0.01 mg/kg/day was increased gradually. After extubation 3 months after the onset of DCM, the propranolol was changed to carvedilol. He received CRT at 11 years old for dyssynchrony of the left ventricle. Further, one patient developed a cerebral infarction, 5 months after the onset of DCM, when her heart failure worsened during the initial induction of carvedilol.

The CE-free survival rate at 2 years was 5% (95%CI 0.7–28) in the early group. In the later group, the CE-free survival rates at 2 years and 15 years were 83% (95%CI 59–91) and 71% (47–87), respectively. There was a significant difference between the two groups ($p < 0.001$) (Fig. 5). On the other hand, the 20-year survival rate in the early and later groups were 5% and 100%, respectively. The survival rate in the later group was significantly higher than that in the early group ($p < 0.001$) (Fig. 6). The use of ACEIs significantly affected the outcome of DCM in infants (hazard ratio 0.152, 95%CI 0.032–0.583, $p = 0.004$), and the use of beta-blockers also affected the outcome of DCM in infants in the multivariate analysis (hazard ratio 0.142, 95%CI 0.026–0.626, $p = 0.008$) (Table 2).

Five years after the onset of DCM excluding heart transplantation in the later group, the LVFS ranged from 9% to 39%, with a median of 30%. The LVDd was 94% to 172% of normal, with a median of 114% of normal ($n = 18$) (Fig. 7). The values of BNP (pg/ml) were as follows: <5.8 in 10 patients, ≥5.8 but <20 in 4, and ≥20 but <100 in 4. However, the cardiac function in one patient with CLBBB improved 2 years after CRT at 11 years old. The LVFS increased from 9% to 25%, and the LVDd decreased from 172% to 119%. On the other hand, the LVFS improved during the use of ACEIs before the induction of carvedilol in 3 patients. The New York Heart Association class in the later group was I in 23 patients, except for one patient with a neurological disturbance. The only surviving patient after Batista operation in the early group was New York Heart Association class II.

Discussion

It has been recognized that some patients with DCM often develop intractable heart failure and need a heart transplantation. The number of donors is limited. Transplantation outside Japan in a child presents the risks and costs that are unnecessary and unacceptable. Infants with DCM should be carefully screened for and offered CRT, mechanical assist device, and heart transplant when feasible. However, their decision might be often critical and difficult in some patients. Although there was only a small number of patients in this study, the outcome in those patients with infantile DCM has improved by the long-term gradually medical supportive care since the 2000s. If possible, a heart transplantation in children should be avoided at young ages with the optimal management.

Treatment for acute severe heart failure due to DCM has recently become more successful due to the addition of PDE III inhibitors and human atrial natriuretic peptides to the conventional therapies from the 2000s. However, worsening heart failure often coincides with the introduction of the beta-blocker carvedilol immediately after the initial acute treatment [11,12]. With this attitude, when faced with increasing severity of

Table 2
Effect on the outcome of infantile DCM.

Medicine	Univariate			Multivariate		
	Hazard ratio	95%CI	*p*-Value	Hazard risk	95%CI	*p*-Value
ACEIs	0.056	0.015–0.160	<0.0001	0.152	0.032–0.583	0.004
Beta-blockers	0.054	0.012–0.165	<0.0001	0.142	0.026–0.626	0.008

DCM, dilated cardiomyopathy; ACEIs, angiotensin-converting enzyme inhibitors; CI, confidence interval.
* In this analysis, the patient who had undergone heart transplantation was classified as an event at that time.

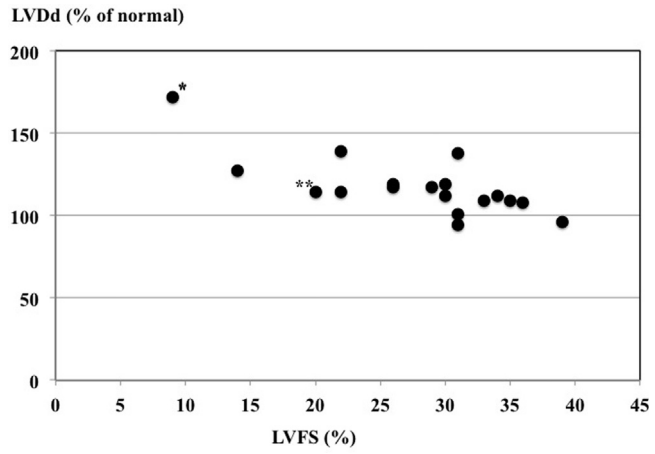

Fig. 7. The left ventricular parameters in the two-dimensional echocardiograms at 5 years after the onset of dilated cardiomyopathy. LVFS, left ventricular fractional shortening; %LVDd, percent of normal left ventricular end-diastolic dimension. *After he underwent cardiac resynchronization therapy at 11 years old for complete left bundle branch block, his LVFS increased from 9% to 25%, and his LVDd decreased from 172% to 119%. **She had undergone mitral valvuloplasty 3 months after the onset of dilated cardiomyopathy.

the heart failure, physicians are tempted to increase the carvedilol dosage resulting in some patients developing intractable heart failure and the need for a heart transplantation. The usual low dose of carvedilol (0.01–0.02 mg/kg/day) immediately after a successful treatment of acute heart failure should be careful to prevent worsening of heart failure. Over-dose and urgent increase in the dose of beta-blockers in severe heart failure patients may be detrimental. One of the problems related to the prognosis of infantile DCM may be the early initiation of carvedilol.

The other point for the survival in this population was to take a long time to initiate support with the use of low-dose catecholamines or PDE III inhibitors, when a low ventricular function persisted after an initial treatment for acute heart failure [13]. It is important to decrease gradually low-dose catecholamines or PDE III inhibitors depending on each patient's condition. Firstly, digoxin is useful for lowering the heart rate. Secondly, ACEIs are useful because they have fewer side effects regarding the hemodynamics than beta-blockers. Our study indicated the usefulness of ACEIs for the outcome. Further, measurement of the BNP level in clinical management became possible in the middle of the 1990s. The BNP level is also a good guide when starting and adjusting beta-blocker therapy in patients with a low left ventricular ejection fraction [14]. Starting beta-blockers might be avoided when the BNP level is more than 400–500 pg/ml. Guided by the BNP level, the dose of the beta-blockers should be gradually increased in patients with severe heart failure [15,16]. It might be good to take time and slowly and carefully carry out the treatment, according to the condition of each patient. We think the induction of beta-blockers should not necessarily be hurried, because their negative inotropic effects are not good in patients with severe heart failure. It is important to know how to use beta-blockers [11]. The LVFS often improved slightly before the re-induction of carvedilol in our experience. It is unknown how dose of carvedilol also improves the left ventricular function in children. The effect should be further investigated based on the dose of the medicine.

Everitt et al. reported a series of children in whom 22% recovered to a normal left ventricular function and size; 51% died or underwent a heart transplantation, and 27% had persistent abnormal echocardiograms 2 years post-acute onset [16]. Further, it was reported that some patients with a normal left ventricular function and size within 2 years of the diagnosis later undergo a heart transplantation or die. On the other hand, the outcome was fair, if the patients survived for more than 2 years after the onset of the disease in our series. Left ventricular reverse remodeling after the onset of DCM in some patients can occur within 2 years [11]. However, the LVDd in some patients in our series increased with their physical development, but the LVFS was preserved. Because the cause of infantile DCM is not uniform, the effects on the medicine and the outcome would be also various. Therefore, further investigation of the cardiac function over the long-term period in this population is needed.

Study limitations

The treatment and care with medicine has remarkably improved over the past 30 years with the medical developments. Because pediatric cardiology at the middle of the 1980s had been on the way to development, the option in treatment and management for heart failure had been limited. Further, the number of the patients in this study was small. The optimal treatment was not uniform, but also various depending on each patient in many points.

Conclusion

The outcome in patients with infantile DCM significantly improved with a careful acute treatment, especially with PDE III inhibitor and chronic treatment using ACEIs for heart failure since the 2000s. Care is needed to avoid initiation or increase of dose of beta blockers in acute stage, corresponding to each patient's condition, to avoid worsening of heart failure. Adopting a long-term supportive treatment during a period of low ventricular function and how to use beta-blockers corresponding to each patient's condition were key to survival.

Conflicts of interest

The authors declare that they have no conflict of interest and no financial support.

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