Dilated Cardiomyopathy: Clinical Significance of Possible Related Factors

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The present study investigates the clinical significance of several possible causative or conditioning factors which have been proposed to be involved in the pathogenesis of dilated cardiomyopathy (DCM). By reviewing the medical records of 68 patients with DCM, we found a definite, and suggestive family history in 16%, and 28%, respectively, and antecedent flu-like symptoms in 43%. A history of hypertension was observed in 35%, habitual alcoholism in 49% and diabetic pattern on glucose tolerance test in 37%. We then classified the study patients into three groups; familial, myocarditic and acquired groups. The familial group showed advanced myocardial damage with the poorest prognosis. Abnormal T-cell subsets in this group suggested that genetically determined abnormal immune response is involved in the development of DCM. In the myocarditic group, endomyocardial biopsy demonstrated mononuclear cell infiltration in 53% and the myocardial damage and prognosis were of intermediate severity. The acquired group showed significantly more frequent histories of hypertension, habitual alcoholism or diabetes than their age- and sex-matched controls, suggesting that they developed the disease in association with these factors. The severity of hemodynamic impairment and myocardial damage was the least extensive and prognosis was relatively favorable in this group.

These different clinical features in the three groups may provide evidence that these factors actually contribute to the development of myocardial damage in DCM and that the condition is a clinical syndrome associated with heterogeneous etiologies or conditioning factors. Determination and management of these factors would be of practical value in treating patients with DCM that has no established therapy against underlying etiologies.

ALTHOUGH dilated cardiomyopathy (DCM) by definition¹ is a condition of unknown cause, it is likely that DCM is a clinical syndrome which is the end result of a wide variety of

etiologic insults to the myocardium. The possible causes or conditioning factors that contribute to the development of DCM include genetic predisposition, viral myocarditis associated with immunological abnormalities, alcohol or other toxic substances, hypertension, pregnancy or the puerperium or endocrine disorders²⁻⁴. These diverse etiologic agents or conditioning factors may explain the wide variety of clinical manifes-

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TABLE 1 FREQUENCIES OF RELATED FACTORS IN DILATED CARDIOMYOPATHY

	Total	Age groups (years)		
		~ 39	40 ~ 49	50 ~
Family history	44	53	45	39
Definite	(16)	(24)	(15)	(13)
Suggestive	(28)	(29)	(30)	(26)
Antecedent flu	43	59	50	29
History of hypertension	35	6	35	52
Habitual alcoholism	49	29	60	52
Diabetes†	37	22	33	45

Values are percent of patients with a factor.

†Glucose tolerance test was performed in 43 patients.

tations, histological findings and long-term prognosis of patients with DCM.

In the present study, we analyzed the etiologic or conditioning factors by retrospectively reviewing medical records. The clinical significance of these factors was then investigated by comparing with clinical features, endomyocardial biopsy findings and long-term prognosis.

SUBJECTS AND METHODS

Study patients

The study group consisted of 68 patients with DCM (54 men and 14 women, mean age 47 ± 13 years) who were seen consecutively at Kurume University Hospital between 1975 and 1985. All patients fulfilled the echocardiographic criteria of left ventricular end-diastolic diameter > 55 mm and fractional shortening $< 30\%$. Patients with underlying coronary artery disease, valvular heart disease, acute myocarditis, hypertrophic cardiomyopathy and other cardiac or systemic diseases involving the heart muscle were excluded from the study. We also excluded those with a history of excessive alcohol intake of 125 ml or more (900 ml or more of Japanese 'sake' rice wine) per day and those who presented systemic hypertension of 160/95 mmHg or more during hospital stay.

Determination of related factors

In an attempt to determine possible causative or conditioning factors that might contribute to the development of DCM, we retrospectively reviewed medical records for; 1) a family history, defined as definite when DCM was documented by 2-dimensional echocardiography and as

suggestive when heart disease or sudden death in relatives was reported, 2) flu-like symptoms occurring within 2 months before the first cardiac manifestation, 3) habitual alcohol intake of less than 125 ml per day, 4) a history of hypertension and 5) 50g glucose tolerance test, assessing the diabetic pattern according to the criteria proposed by the Japan Diabetes Association (ie, glucose levels at one and two hours after glucose ingestion exceed 160 mg/dl, and 130 mg/dl respectively). Histories of alcohol, hypertension and the result of the glucose tolerance test were additionally assessed in healthy controls who were admitted to the hospital for routine health checks, selecting two controls for each patient matched for sex and age (within 5 years).

Endomyocardial biopsy

An endomyocardial biopsy sample was obtained from each of 55 patients with DCM from the right side of the ventricular septum. The myocardial cell diameter was determined by measuring the distance across the cell at its most narrow plane across the nucleus in hematoxylin-eosin-stain slices. At least 30 cells from each biopsy were measured and the diameters were averaged to determine the value for each patient. The percent fibrosis was evaluated in Azan-stain slices by the point-counting method. Patterns of fibrosis were classified into three types according to Anderson et al.⁵ Mononuclear cell infiltration was taken as positive when more than five cells were observed in the high power field ($250 \times 250 \mu$).

TABLE II FREQUENCIES OF HISTORY OF HYPERTENSION, HABITUAL ALCOHOLISM AND DIABETIC PATTERN IN DILATED CARDIOMYOPATHY (DCM) AND AGE- AND SEX-MATCHED CONTROLS

	History of hypertension	Habitual alcoholism	Diabetic pattern
Total			
DCM	35	49	37
Controls	36	42	15
Acquired group			
DCM	65*	74*	40*
Controls	37	48	17

Values are percent of patients with a factor.

* $p < 0.05$, as compared with controls.

Long-term follow-up study

Fifty-eight patients who had been admitted to the hospital before August 1984 were followed-up until death or at least for a minimum of one year (mean follow-up years 2.5 ± 2.2 years). Survival curves were plotted by actuarial life table analysis. Statistical analysis and calculation of a relative risk based on the survival data were performed by the method of Mantel and Haenszel.⁶

Lymphocyte subsets

Lymphocyte subsets were analyzed by a laser flow cytometry (Spectrum III, Ortho Diagnostic System). Monoclonal antibodies used as membrane markers were; OKT 4, OKT 8, OKT 11 (Ortho Diagnostic System), antihuman Leu-11a (Becton-Dickinson). We also used TA75 antibody which was developed in our laboratory to identify interleukin 2 receptor.

Fig. 1. Two brothers of familial dilated cardiomyopathy (DCM) whose parents are cousins. Elder brother died from heart failure 15 years ago at age 16 and autopsy findings were compatible with DCM. Younger brother (25 years old) is currently suffering from heart failure and intractable, recurrent ventricular tachycardia with left ventricular dilatation (68 mm) and depressed fractional shortening (10%). Both patients show quite similar electrocardiographic patterns of QS in leads V_1 through V_4 and negative T wave in V_5 and V_6 . Microscopically, the elder brother presents a loss of myocardial cell with moderate fibrosis in the autopsy specimen and the younger brother demonstrates extensive interfiber and partly plexiform fibrosis in the biopsy specimen.

Fig. 2. Autopsied patients (46 years old female) possibly associated with myocarditis. Her father was also reported to have died of heart disease. The patient developed fever, myalgia and facial nerve palsy 4 years ago, followed by two episodes of syncopal attack. She was admitted to the hospital with heart failure and showed left ventricular dilatation (60 mm) and depressed fractional shortening (10%). Electrocardiogram presents right bundle branch block and left axis deviation. Autopsy specimen demonstrates persistent mononuclear cell infiltration in the area of extensive fibrosis.

Detailed procedures for lymphocyte isolation, cell staining with monoclonal antibody and flow cytometry were described in the previous reports.⁷ The results were compared between DCM patients and healthy controls, selecting two volunteers for each patients matched for sex and age (within 5 years).

RESULTS

Related factors of DCM

Table I presents the frequency of related factors obtained by reviewing medical records. Familial occurrence was definite in 16% of DCM patients and suggestive in a further 28%. The familial occurrence tended to be more frequent

Fig. 3. A representative patient from the acquired group (57 years old male) who presented a history of hypertension and diabetes. Although he had left ventricular dilatation (73 mm) and depressed fractional shortening (5%), his electrocardiogram shows no decrease in QRS amplitude despite right bundle branch block and left axis deviation. The biopsy specimen demonstrates perivascular fibrosis with minimal loss of myocardial cell.

in younger patients. Flu-like symptoms preceding cardiac manifestations were noted in 43% and were more frequently found in younger patients. History of hypertension was reported in 35%, although they were normotensive during the hospital stay. Habitual alcohol intake, though less than 125 ml per day, was noted in 49% of patients. The histories of hypertension and alcohol were more frequent in elderly patients. Of 43 patients who had a glucose tolerance test, a diabetic pattern was observed in 37%, and was more frequent in the elderly patients.

In the analysis of the number of related factors per patient, 28 patients had two factors, 14 three and 4 had four factors. On the other hand, 18 patients had a single factor and 4 had none of the factors.

Classification of DCM according to the related factors

In an attempt to determine the role of these

TABLE III CLINICAL FEATURES AND ENDOMYOCARDIAL BIOPSY FINDINGS IN THE THREE GROUPS OF DILATED CARDIOMYOPATHY

	Familial (n = 14)	Myocarditic (n = 18)	Acquired (n = 30)
Age (years)	41 ± 15	42 ± 13	52 ± 9**††
Sex (male : female)	11 : 3	10 : 8	29 : 1††
Blood pressure (mmHg)			
Systolic	111 ± 14	114 ± 11	122 ± 18
Diastolic	74 ± 12	73 ± 12	78 ± 15
Cardiothoracic ratio (%)	61 ± 6	59 ± 5	60 ± 8
SV ₁ + RV _s (mm)	25 ± 12	41 ± 19*	41 ± 17**
LVDd (mm)	65 ± 5	64 ± 5	68 ± 9
Fractional shortening (%)	10 ± 6	15 ± 5*	11 ± 6†
IVST + PWT (mm)	19 ± 3	20 ± 3	22 ± 4*
LVEDP (mmHg)	22 ± 9	16 ± 9	14 ± 8*
Myocardial cell diameter (μ)	18 ± 3	17 ± 3	20 ± 3†
Percent fibrosis	25 ± 6	24 ± 10	18 ± 8*
Patterns of fibrosis (%)			
Perivascular	36	33	54
Plexiform	36	53	21†
Interfiber	45	13	46†
Mononuclear cell Infiltration (%)	10	54*	4††

Values are number of patients, mean ± SD or percent.

p* < 0.05, *p* < 0.01, as compared with familial group.

†*p* < 0.05, ††*p* < 0.01, as compared with myocarditic group.

4 patients with no factor and 2 with familial heart block were excluded.

Endomyocardial biopsy findings were analysed in 55 patients.

Abbreviations: LVDd = left ventricular diameter at end-diastole; IVST = interventricular septal thickness; PWT = posterior wall thickness; LVEDP = left ventricular end-diastolic pressure.

related factors, DCM patients were classified into three groups; familial, myocarditic and acquired groups. The familial group included 9 patients with definite and 5 with suggestive familial occurrence but with no other factors. The myocarditic group consisted of 18 patients with antecedent flu-like symptoms, and some clinical and electrocardiographic evolution suggestive of myocarditis. Thirty patients with a history of hypertension, habitual alcohol intake and/or with diabetic pattern were classified as being in the acquired group, unless they were already classified as being in either in the familial or myocarditic groups. Four patients without any factor and 2 associated with familial heart block were excluded from further analysis. In the acquired group, frequencies of a history of hypertension, alcohol and diabetic pattern were 65%, 74%, and 40%, respectively, which were significantly higher than those in age- and sex-matched controls (Table II). Representative patient

profiles from the 3 groups are illustrated in Figs. 1 to 3.

Clinical features and endomyocardial biopsy findings in the three groups (Table III).

Of the 3 groups, the acquired group consisted of significantly older patients and these were predominantly male. Systolic and diastolic blood pressure did not differ significantly among the three groups. Cardiothoracic ratio and echocardiographic left ventricular diameter at end-diastole were not different among the three groups. Fractional shortening was significantly higher in the myocarditic group, but still markedly depressed. SV₁ + RV_s and left ventricular wall thickness (summed thickness of the ventricular septum and posterior wall) were significantly greater, while left ventricular end-diastolic pressure was significantly lower in the acquired group when compared with the familial group.

TABLE IV PREDICTORS OF LONG-TERM PROGNOSIS OF DILATED CARDIOMYOPATHY

	2 years survival (%)	Relative risk
Acquired	79	
Myocarditic	50	3.0
Familial	36	6.0*
CTR < 60%	87	
≥ 60%	51	4.7*
Habitual (+)	81	
alcoholism (-)	49	3.7*
Family (-)	77	
history (+)	47	3.4*
SV ₁ + RV _s ≥ 35 mm	85	
< 35 mm	59	3.4

**p* < 0.05

Abbreviations: CTR = Cardiothoracic ratio

TABLE V FREQUENCY OF LYMPHOCYTE SUBSETS IN DILATED CARDIOMYOPATHY (DCM) AND AGE- AND SEX-MATCHED CONTROLS

	DCM	Controls
OKT 11 (<i>n</i> = 30)	77 ± 7	76 ± 6
OKT 4 (<i>n</i> = 30)	44 ± 8	40 ± 8
OKT 8 (<i>n</i> = 30)	22 ± 6***	28 ± 6
OKT 4/8 (<i>n</i> = 30)	2.1 ± 0.7***	1.5 ± 0.6
Leu-11a (<i>n</i> = 13)	9.2 ± 4.1**	15.0 ± 7.0
TA 75 by Con-A (<i>n</i> = 9)	41 ± 16**	60 ± 8

Values are mean ± SD

p* < 0.01, *p* < 0.001 as compared with controls.

Abbreviations: Con-A = Concanavalin-A

Myocardial cell diameter was greater and fibrosis was less extensive in the acquired group. In the analysis of patterns of fibrosis, perivascular and interfiber patterns tended to be more frequent in the acquired group, while the plexiform pattern was more frequently observed in the myocarditic group. Mononuclear cell infiltration was observed in 54% of those with the myocarditic group.

Long-term prognosis (Table IV)

During the follow up of 2.5 ± 2.2 years, 29 of 58 patients died, 18 from heart failure, 8 from sudden death and 3 from non-cardiac causes.

Fig.4. The OKT4/OKT8 (helper/suppressor) ratio of T-lymphocyte in the three groups of dilated cardiomyopathy. The familial group shows a significantly higher ratio than the acquired group with 50% of the group presenting an abnormally high ratio, exceeding normal range (within ± 2 SD of the mean value of the control subjects).

One- and 2-year survival rates from cardiac death were 80% and 65%. In the three subgroups, the familial group presented the poorest prognosis with a relative risk of cardiac death of 6.0 as compared with the acquired group. Other significant predictors of cardiac death were cardiothoracic ratio, habitual alcohol intake and a positive familial history, which included definite and suggestive cases.

Lymphocyte subsets (Table V)

Frequency of OKT 11 (total T-cell) and OKT 4 (helper/inducer) did not differ between DCM patients and the age- and sex-matched

controls. However OKT8 (suppressor/cytotoxic) was significantly reduced and a OKT 4/OKT 8 ratio was significantly higher in DCM patients. Leu-11a (natural killer cell) and TA75 (cells with interleukin 2 receptor) positive cells by concanavalin-A stimulation were also significantly lower in DCM patients.

In the three subgroups of DCM, the familial group showed a significantly higher OKT 4/OKT 8 ratio than the acquired group and 50% of them demonstrated an abnormally high ratio exceeding the normal range. Two of the 8 patients with the myocarditic group had an abnormally high ratio, but 92% of the acquired group presented a normal value (Fig. 4).

DISCUSSION

Possible related factors of DCM

In the present study, we attempted to clarify possible related factors of DCM that might associate underlying etiology or contribute to its development or aggravation.

It has been generally considered that there is little evidence of a familial tendency for DCM. However, several reports⁸⁻¹¹ have described familial DCM. Among 161 children with DCM, Greenwood et al.¹² found that 8.1% had a definite family history of heart disease. In the recent comprehensive study of Michels et al.¹³ 6.5% of DCM patients were determined to be familial. They emphasized that a positive family history may not always be readily apparent and that familial DCM is not rare if one makes extensive efforts to examine the relatives of patients. In the studies of the natural history of DCM by Fuster et al.¹⁴ and Unverferth et al.¹⁵ 20% and 6% of patients were reported to show a positive family history. In the present study, we found that 16% of DCM patients had relatives affected by DCM and the other 28% showed family members who manifested heart disease or sudden death suggesting familial occurrence. We therefore propose that genetic factors play an important role in the development of DCM in certain patients. Further studies will be needed, however, to clarify whether the genetic factors are directly causative or merely predispositions, which determine susceptibility for viral infection, alcohol or other related factors.

The mode of inheritance in the familial DCM is unknown, although several authors have suggested an autosomal dominant inheritance^{8,9,11,13} by tracing affected relatives over two or three

generations. In the present study, some patients had two or three affected siblings but no patients presented affected relatives over two generations. On the other hand, Yamaguchi et al.¹⁶ studied a consanguinity rate in 35 DCM patients and found the rate of 35%, which was considerably higher than in the general population in Japan. They, therefore, proposed a possible association of autosomal recessive inheritance in DCM.

The hypothesis that DCM often results from previous recognized or unrecognized viral myocarditis has long attracted many investigators^{2,3,17} The evidence supporting the hypothesis includes documentation of progression from acute viral myocarditis to chronic DCM, high incidence of enteroviral antibodies in the sera of DCM patients and identification of persistent inflammation in the heart of patients with DCM. In the present study, we noted antecedent flu-like symptoms before cardiac manifestation in 43% of patients, despite an exclusion of acute viral myocarditis. The symptoms were more frequent in younger patients. Endomyocardial biopsy revealed that 19% of patients had persistent mononuclear cell infiltration. The figure is nearly consistent with the result of the multicenter study, which was 17%, projected by the Idiopathic Cardiomyopathy Research Committee in Japan.¹⁸ Thus, around 20% of patients with DCM could be referred to as having chronic and persistent myocarditis.

It has long been recognized that people who consume large amounts of alcohol develop signs of congestive heart failure, which often resembles DCM.¹⁹ Although it is still uncertain whether excessive alcohol consumption itself leads to heart failure, patients whose daily alcohol consumption exceed 125 ml (900 ml in Japanese rice wine) for 10 years are called alcoholic cardiomyopathy and usually are excluded from a diagnosis of DCM. However, there remains a possibility that habitual alcohol intake of even a smaller amount could cause a conditioning factor that lowers the resistance of the myocardium to other noxious agents or whose depressant effect on an already ailing myocardium might result in worsening of a mild or subclinical myocardial abnormality. In the present study, habitual alcohol intake of less than 125 ml was observed in 52% of DCM patients and in 75% of the acquired group, which was significantly higher than their age- and sex-matched controls. These patients with habitual

alcohol intake had a more favorable prognosis. These observations imply that daily alcohol intake, even of small amount, is a significant conditioning factor of DCM.

It is well known that patients with long-standing, sustained hypertension finally experience left ventricular dilatation and heart failure. We excluded these patients in the terminal stage of hypertension, and included only those who were normotensive during the hospital stay. Nevertheless, a history of hypertension was noted in 36% of patients with DCM, and this was increased to 68% in the acquired group, which was significantly higher than their age- and sex-matched controls. There has been, however, much debate regarding the role of hypertension in the genesis of DCM²⁰⁻²³. As these patients present mild hypertension at some stage in the course of DCM and are no longer hypertensive at the time of diagnosis, it is clear that hypertension is not a sole cause of their heart failure. Most authors have postulated that hypertension is not a primary cause, but is secondary to congestive heart failure. On the other hand, several authors have described hypertension as a cause of DCM, as these patients occasionally develop high blood pressure following recovery from heart failure. In our previous studies²⁴ we have demonstrated that the majority of DCM patients with a history of hypertension have hypertensive retinal change, although mild, and show a greater increase in blood pressure during exercise when compared with those without the history. Therefore, we believe that hypertension is a significant conditioning factor that acts in concert with other factors to produce severe myocardial damage.

Although Rubler et al²⁵ proposed the concept of diabetic cardiomyopathy in 1972, there still remains a controversy regarding the relation of diabetes to DCM²⁶. Recent studies by Factor et al²⁷ have reemphasized the role of diabetes, in association with hypertension, in the development of DCM. However it is rare to find advanced diabetic patients in DCM and there were no patients who required insulin in the present study. On the other hand, 39% of patients presented a diabetic pattern in the glucose tolerance test. The frequency of the diabetic pattern was significantly higher in the DCM patients with 50 years old or older, and more so in those of the acquired group than the controls. These observations imply that diabetes could not be ignored, at least as a conditioning

factor of DCM.

Of 68 patients with DCM in the present study, we could find no related factors in only 4 patients. In contrast, 68% of patients had two or more factors. The findings agree with the concept proposed by Goodwin²⁸ that DCM is a multifactorial disease in which multiple causes or conditioning factors are involved in the development of myocardial damage.

The relationship between related factors and clinical manifestations of DCM

In order to determine the role of these related factors, we classified the study patients into the familial, myocarditic and acquired groups and compared clinical manifestations, including endomyocardial biopsy finding and long-term prognosis. By age and sex, the acquired group was older and was predominantly male. Thus the contribution of alcohol, hypertension and diabetes would be one of reasons why elderly men are more frequently affected with DCM. Systolic and diastolic blood pressure readings did not differ significantly among the three groups, although the acquired group included patients with a history of hypertension. The three groups did not differ in cardiothoracic ratio and echocardiographic end-diastolic diameter of the left ventricle. Fractional shortening was significantly greater in the myocarditic group, but still severely depressed. Therefore dilatation and impairment of systolic function of the left ventricle seemed to be nearly equivalent among the three groups.

On the other hand, $SV_1 + RV_5$, left ventricular wall thickness and myocardial cell diameter were greater in the acquired group. Hence some degree of compensatory myocardial hypertrophy seemed to have taken place in the acquired group. In contrast, patients with the familial group presented a higher left ventricular end-diastolic pressure and a greater degree of myocardial fibrosis, implying that they had the most extensive myocardial damage. Patterns of myocardial fibrosis also differed among the three groups. The plexiform pattern tended to be more frequent in the myocarditic group, while perivascular and interfiber patterns were more commonly observed in the acquired group. In the myocarditic group, mononuclear cell infiltration was noted in 54% of patients, while hemodynamic and myocardial impairment was of intermediate severity.

In the long-term follow up study, the familial

group showed the poorest prognosis with a relative risk of cardiac death of 6.0, compared with the acquired group. Alcohol intake, again, was a significant factor determining the prognosis, in addition to cardiothoracic ratio. The result indicates that the prognosis of DCM may depend on conditioning or etiological factors.

Lymphocyte subsets in DCM

There is an increasing interest in the role of immunological abnormalities in the development of DCM.¹⁷ The present study further supported the previous observations that patients with DCM have reduced frequency of suppressor T-cells²⁹ and of natural killer cells.^{30,31} Significantly lower frequency of the lymphocytes with interleukin 2 receptor after concanavalin-A stimulation was consistent with the previous reports of Fowles et al³² and Eckstein et al³³ that activity of suppressor T-cells is also depressed in DCM patients. In addition, the OKT 4/OKT 8 ratio was significantly higher in the familial group, implying that abnormal T-cell function is genetically determined. O'Connell et al⁹ also reported patients with familial DCM associated with abnormal cell-mediated immunity. In the analysis of histocompatibility antigen (HLA), Anderson et al³⁴ found increased frequency of HLA B27 and DR4 halotypes and decreased frequency of HLA DR6Y halotype in DCM patients. This collective evidence suggests that genetically determined abnormality in the immune response play a role in the pathogenesis of DCM in some patients.

On the other hand, in this study the myocarditic group did not show a definite abnormality of the OKT4/OKT8 ratio, although one patient presented an extremely high ratio. We might then consider that immunological defects other than T-cell function are involved in the progression from myocarditis to DCM.

Clinical implications

Although we classified the study patients arbitrarily into 3 groups, based on the related factors determined retrospectively by reviewing medical records, each group presented some characteristic clinical manifestations. Patients with familial DCM showed an advanced myocardial involvement with the poorest prognosis. Abnormal T-cell subsets in this group suggested a role of genetically determined abnormal immune

response in the development of DCM. Of those who were suggested to be associated with myocarditis, 53% showed mononuclear cell infiltration. The severity of myocardial damage and the prognosis of this group were intermediate. In contrast, patients with the acquired group who were supposed to develop the disease in association with alcohol, hypertension and/or diabetes presented less advanced hemodynamic impairment and myocardial damage. The long-term prognosis was relatively favorable in this group.

These different clinical features in the three groups provide evidence that the related factors significantly contribute to the development of myocardial damage in DCM. The present study, thus, indicates that DCM is a syndrome associated with heterogeneous etiologies or conditioning factors. Considerable variability from patient to patient of clinical features, histological findings and long-term prognosis may reflect these diverse etiologic agents or conditioning factors. This implies that there may be no abnormalities which are linked to the etiology and are at the same time common to all patients with DCM. An example would be the present result of the OKT4/OKT8 ratio where only 23% showed an abnormally high value. Inconsistent results of the ratio in previous studies^{29,31} may be explained by the heterogeneity of the patient population. On the other hand, it should be noted that these related factors are not necessarily the primary causes of myocardial abnormality of DCM, but may be conditioning factors which worsen already ailing myocardium from undetermined pathogenesis. Nevertheless, determination and management of these related factors would be of practical value in treating patients with DCM that has no established therapy against underlying etiologies.

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