Familial Aggregation of Dilated Cardiomyopathy
— Evaluation of Clinical Characteristics and Prognosis —

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To investigate the prevalence, clinical characteristics, and prognosis of familial cases of idiopathic dilated cardiomyopathy (IDC), family screenings were carried out in 117 IDC patients and their relatives. Familial occurrence was suspected in 29 families (25%). Ten families (9%) with 24 patients were confirmed to be familial, but the other 19 families (16%) remained suspected. The age at the time of diagnosis was lower and the cardiac symptoms tended to be milder in the familial group than in the non-familial group, but there were no differences in other clinical parameters. There was also no difference in the survival rate. However, when only NYHA class III and IV patients were selected, the 1-year and 5-year survival rates were lower in the familial group than in the non-familial group. Congestive heart failure was the most common cause of death in the non-familial group, while sudden death was the most common cause of death in the familial group. Among familial IDC patients who were deceased, the left ventricular end-diastolic pressure was higher and the cardiac index was lower at the time of diagnosis than those in patients who were still alive. We conclude that, since the prognosis of familial IDC patients is poor once their cardiac symptoms become severe, early diagnosis and treatment are extremely important.
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IDIOPATHIC dilated cardiomyopathy (IDC) is a cardiac disease that is characterized by the dilation and impaired systolic function of ventricles^{1–4}. Although several factors, such as myocarditis, alcohol intake, pregnancy and puerperium, arterial hypertension, and genetic transmission, are known to be predisposing to IDC, the etiology of this disease remains unknown^{1,5–7}. Particularly with regard to hereditary predisposition, most cases of IDC are believed to be sporadic. Recently, the existence of familial occurrence of this disease has been described. However, the reported prevalence of familial

IDC has varied from 2 to 30%^{8–16} and the clinical characteristics and prognosis remain uncertain.

Therefore, the purpose of our study was to analyze the prevalence, mode of inheritance, clinical characteristics, and prognosis of familial IDC patients.

METHODS

We studied 117 patients with IDC (90 men, 27 women) from 117 families who visited our institution from November 1973 to December 1990.

Detailed family histories were obtained, and family screenings were carried out. These 117 probands and their 1,237 relatives (1st–4th-grade relatives) were enrolled in

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this study. The mean age of the 117 probands at the time of diagnosis was 47 ± 16 years.

The diagnosis of IDC was based on echocardiography, cardiac catheterization, myocardial biopsy or autopsy, according to the report of the WHO/ISFC task force⁴. The criteria for the diagnosis of dilated cardiomyopathy included left ventricular end-diastolic dimension of more than 56 mm and fractional shortening of less than 28%, as determined by echocardiography, or left ventricular ejection fraction below 45% by left ventriculography. Echocardiographic studies were performed in 116 probands, and 84 underwent left ventriculographic studies. Patients with any of the following conditions were excluded: ischemic heart disease with significant stenosis of the coronary arteries, valvular disease, cor pulmonale, congenital heart disease, neuromuscular disease and other systemic diseases. We also excluded patients with dilated phases of hypertrophic cardiomyopathy, who had hypertrophic phases in their past with typical disarray in biopsy specimens, or who had hypertrophic cardiomyopathy patients among their relatives.

Physical examinations, electrocardiography, and echocardiography were performed in 51% of the relatives, who were alive and agreed to participate at the time of this investigation. Twenty-five percent of the relatives were dead and 24% did not agree to participate. If the existence of myocardial disease was suspected in the relatives, cardiac catheterization, and cardiac biopsy were carried out whenever possible. Further information regarding affected relatives was obtained from their attending physicians when such relatives lived far from our hospital and were followed by other medical centers. According to the proposal of Sekiguchi et al¹² we divided the familial IDC families into two categories. When more than one member of the 1st-grade relatives (parents, siblings, offspring) of the probands was confirmed to be affected, based on the criteria mentioned above, we termed the family, as a "confirmed familial IDC family". Families with 1st-grade relatives who were suspected to be affected, but were not examined sufficiently to confirm the diagnosis, or who had died of unknown cardiac

disease, were called "suspected familial IDC families". On the other hand, families with no affected relatives, neither suspected nor confirmed, were called "non-familial IDC families". Non-familial IDC families had no family history of unknown cardiac disease or death, and the relatives we examined had no evidence of dilated cardiomyopathy. We performed physical examination, electrocardiography, and echocardiography in at least 3 members of the 1st-grade relatives in non-familial IDC families, and whenever possible, we performed these tests in more than 4 family members. Finally, the prevalence and the modality of inheritance of familial IDC patients were investigated.

Clinical Parameters

Age, gender, New York Heart Association classification (NYHA), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), cardiothoracic ratio on chest x-ray (CTR), the severity of arrhythmias (Lown's classification) by Holter electrocardiography, echocardiography measurements, and hemodynamic parameters were obtained in the "confirmed familial IDC patients" at the time of diagnosis. According to the method described by Sahn et al⁷ left ventricular end-diastolic dimension (LVDd), left ventricular end-systolic dimension (LVDs), and fractional shortening (%FS) were measured by M-mode echocardiography under the observation of two-dimensional echocardiography. We used the pulmonary capillary wedge pressure (PCWP), cardiac index (CI), and left ventricular end-diastolic pressure (LVEDP) obtained by cardiac catheterization as hemodynamic parameters. These parameters were compared between the confirmed familial IDC patients and non-familial IDC patients.

Prognosis

The five-year survival rates of the familial IDC group and the non-familial IDC group were calculated by the Kaplan-Meier method, and the incidences of the causes of death (death due to congestive heart failure, sudden cardiac death, and death due to non-cardiac disease) were calculated. Sudden cardiac death was defined as "natural death due to cardiac causes, heralded by abrupt

Fig.1. Prevalence of familial dilated cardiomyopathy among 117 families. Confirmed familial dilated cardiomyopathy patients (familial group) consisted of 10 probands and 14 confirmed relatives. IDC: idiopathic dilated cardiomyopathy

TABLE I CLINICAL FINDINGS IN FAMILIAL DILATED CARDIOMYOPATHY PATIENTS (familial group) AT THE TIME OF DIAGNOSIS

Family No.	Case No.	Age	Sex	NYHA (°)	CTR (%)	Rhythm	Dd (mm)	Ds (mm)	%FS (%)	pathological findings fibrosis	degeneration	Death	
1	1	16	M	1	51	NSR	67	53	21	mild	none	CHF	
	2	25	M	1	51	NSR	68	58	15	mild	none		
2	3	46	M	4	56	NSR	72	60	17	moderate	none		
	4	34	F	3	63	NSR	72	65	10	—	—		
3	5	22	M	1	47	NSR	60	47	22	mild	mild	CHF	
	6	18	M	1	—	NSR	60	50	17	—	—		
4	7	51	F	3	53	NSR	58	51	12	mild	none		
	8	28	M	1	44	NSR	56	45	20	mild	none		
5	9	41	M	2	57	NSR	59	44	25	moderate	none	CHF	
	10	73	F	3	64	NSR	68	60	12	—	—		
6	11	46	M	1	60	NSR	85	80	6	—	—		
	12	39	M	2	79	NSR	68	63	7	—	—		
7	13	51	M	2	50	NSR	66	55	17	mild	none	SD	
	14	54	F	2	—	NSR	62	50	19	—	—		
8	15	45	M	3	50	NSR	65	60	8	—	—		
	16	56	F	2	65	Af	63	49	22	moderate	maderate		
9	17	61	F	3	59	Af	57	46	19	moderate	moderate	CHF	
	18	52	F	3	56	NSR	65	58	11	mild	none		
10	19	38	M	2	60	RBBB	—	—	—	—	—		CHF
	20	37	M	3	64	Af	60	49	18	severe	severe		
11	21	43	F	3	55	3-AVB	60	52	13	severe	moderate	CHF	
	22	15	M	3	66	NSR	—	—	—	—	—		
12	23	14	M	2	58	NSR	—	—	—	—	—		SD
	24	16	F	2	56	NSR	—	—	—	—	—		
Mean		38		2.2	58		65	55	16				
± S.D.		16		0.8	8		7	9	6				

Af: atrial fibrillation, 3-AVB: complete atrioventricular block, CHF: death due to congestive heart failure, CTR: cardiothoracic ratio, Dd: left ventricular end-diastolic dimension, Ds: left ventricular end-systolic dimension, %FS: fractional shortening, F: female, M: male, NSR: normal sinus rhythm, NYHA: New York Heart Association classification, RBBB: right bundle branch block, SD: sudden cardiac death.

TABLE II COMPARISON OF CLINICAL FINDINGS, AND ECHOCARDIOGRAPHIC AND HEMODYNAMIC MEASUREMENTS BETWEEN FAMILIAL DILATED CARDIOMYOPATHY PATIENTS (familial group) AND NON-FAMILIAL DILATED CARDIOMYOPATHY PATIENTS (non-familial group) AT THE TIME OF DIAGNOSIS

	familial group (n=24)	non-familial group (n=88)	P Value
Age (yr)	38±16	50±14	p<0.05
Sex	M 1.7 : F 1	M 3.6 : F 1	ns
NYHA 1, 2°	58%	40%	ns
NYHA 3, 4°	42%	60%	ns
SBP (mmHg)	115±20	125±23	ns
DBP (mmHg)	69±13	79±21	ns
HR (bpm)	72±16	84±17	ns
CTR (%)	58±8 ^{*1)}	58±9	ns
Holter ECG			
Lown grade 4	64%	63%	ns
Echo and Hemodynamics			
Dd (mm)	65±7 ^{*2)}	66±7	ns
Ds (mm)	55±9 ^{*2)}	56±9	ns
%FS (%)	16±6 ^{*2)}	16±6	ns
LVEDP (mmHg)	17±11 ^{*3)}	15±8 ^{*5)}	ns
CI (l/min per m ²)	2.7±0.9 ^{*4)}	2.8±0.8 ^{*5)}	ns

CI: cardiac index, CTR: cardiothoracic ratio, DBP: diastolic blood pressure, Dd: left ventricular end-diastolic dimension, Ds: left ventricular end-systolic dimension, ECG: electrocardiography, F: female, %FS: fractional shortening, HR: heart rate, LVEDP: left ventricular end-diastolic pressure, M: male, ns: not significant, NYHA: New York Heart Association classification, SBP: systolic blood pressure.

^{*1)}n=22, ^{*2)}n=20, ^{*3)}n=13, ^{*4)}n=17, ^{*5)}n=74

loss of consciousness within 1 h of the onset of acute symptoms in an individual, in whom the time and mode of death was unexpected".¹⁸ In the case of a patient who had already been admitted to the hospital, death which occurred within 1 h of the onset was called sudden cardiac death only when the patient's condition was improving and his or her death was unexpected.

The familial IDC group was further divided into patients who were presently alive and deceased patients, and the clinical parameters in the two groups at the time of diagnosis were compared.

Statistical Analysis

Statistical analysis was performed by Student's t test and the χ^2 test. The Kaplan-Meier method was used to evaluate the survival rate. The data are presented as the mean±SD. P values below 0.05 were considered to indicate statistical significance.

RESULTS

1. Prevalence and Modality of Inheritance of

Familial Dilated Cardiomyopathy

Among the 117 families of the 117 probands, familial occurrence was confirmed in 10 families (9%) (Fig. 1). In these 10 families, 24 patients (10 probands and 14 1st-grade relatives) were eventually confirmed to be IDC. These 24 patients were defined as "confirmed familial IDC patients" (familial group). Table I shows the clinical parameters at the time of the diagnosis of the confirmed familial IDC patients. In these 10 families, an additional 15 relatives (1st~4th-grade relatives) were suspected, but not confirmed, to be affected (Fig. 1). Nineteen families (16%) with 1st-grade relatives who were suspected, but not confirmed to be affected, were defined as "suspected familial IDC families" (19 confirmed probands, 22 suspected relatives). The total number of familial IDC families (including both suspected and confirmed families) was 29 (25%). None of the 1st-grade relatives in the remaining 88 families were even suspected of being affected, and these families were called "non-familial IDC families".

A three-to-four generation pedigree of

Fig.2. Survival rate curves of familial dilated cardiomyopathy patients (familial group) and non-familial dilated cardiomyopathy patients (non-familial group). There was no difference between the two groups.

Fig.3. Survival rate curves of familial dilated cardiomyopathy patients (familial group) and non-familial dilated cardiomyopathy patients (non-familial group) in New York Heart Association (NYHA) Class III or IV. The 1-year and 5-year survival rates in the familial group were significantly lower than those in the non-familial group.

Fig.4. Causes of death in familial dilated cardiomyopathy patients (familial group) and non-familial dilated cardiomyopathy patients (non-familial group). CHF: death due to congestive heart failure, SD: sudden cardiac death.

each familial IDC family was constructed. Six families showed an autosomal dominant pattern of transmission. An autosomal recessive pattern or an autosomal pattern with incomplete penetrance was suspected in 4 families.

2. Comparison of Clinical Parameters Between Familial and Non-Familial Dilated Cardiomyopathy Patients

Table II compares the clinical parameters at the time of diagnosis in familial (familial

group) and non-familial IDC patients (non-familial group). The mean age at the time of diagnosis was significantly lower in familial IDC patients than in non-familial IDC patients (38 ± 16 vs 50 ± 14 years old, $p < 0.05$). The cardiac symptoms, classified by NYHA functional class, tended to be milder in the familial group than in the non-familial group, but this difference was not significant. The other parameters, such as SBP, DBP, HR, CTR, Lown's classification, echocardiographic measurements, and hemodynamic

TABLE III COMPARISON OF CLINICAL FINDINGS, AND ECHOCARDIOGRAPHIC AND HEMODYNAMIC MEASUREMENTS BETWEEN THE PATIENTS WHO WERE ALIVE AND THE DECEASED PATIENTS OF FAMILIAL DILATED CARDIOMYOPATHY GROUP (familial group) AT THE TIME DIAGNOSIS

	Alive (n=13)	Deceased (n=11)	P Value
Age (yr)	38±14	39±19	ns
Sex	M 10 : F 3	M 5 : F 6	ns
NYHA 1, 2°	85%	27%	p<0.05
NYHA 3, 4°	15%	73%	p<0.05
SBP (mmHg)	120±18	108±21	ns
DBP (mmHg)	71±15	66±11	ns
HR (bpm)	69±14	78±20	ns
CTR (%)	56±10 ^{*1)}	60±5	ns
Holter ECG			
Low grade 4	56%	80%	ns
Echo&Hemodynamics			
Dd (mm)	65±8	64±6 ^{*4)}	ns
Ds (mm)	54±10	56±7 ^{*4)}	ns
%FS (%)	17±6	13±5 ^{*4)}	ns
PCWP (mmHg)	11±4 ^{*2)}	26±3 ^{*5)}	p<0.001
LVEDP (mmHg)	11±5 ^{*3)}	30±11 ^{*5)}	p<0.001
CI (l/min per m ²)	3.1±0.8 ^{*2)}	1.9±0.3 ^{*5)}	p<0.0001

CI: cardiac index, CTR: cardiothoracic ratio, DBP: diastolic blood pressure, Dd: left ventricular end-diastolic dimension, Ds: left ventricular end-systolic dimension, ECG: electrocardiography, F: female, %FS: fractional shortening, HR: heart rate, LVEDP: left ventricular end-diastolic pressure, M: male, ns: not significant, NYHA: New York Heart Association classification, SBP: systolic blood pressure.

^{*1)}n=11, ^{*2)}n=12, ^{*3)}n=8, ^{*4)}n=7, ^{*5)}n=5

measurements, did not differ between the two groups.

3. The Prognosis and Causes of Death in Familial and Non-Familial Dilated Cardiomyopathy Patients

Eleven patients (45.8%) in the confirmed familial IDC families died during the mean follow-up period of 1,678 days. On the other hand, 34 patients (38.6%) in the non-familial group died during the follow-up period of 1,673 days. Fig. 2 shows the survival rate curves calculated by the Kaplan-Meier method. There was no difference in the 5-year survival rate between familial IDC patients (48%) and non-familial IDC patients (64%). However, when only the NYHA class III and IV patients were selected, both the 1-year and 5-year survival rates were significantly worse in the familial group than in the non-familial group (1-year survival rate 56% vs 88%, p<0.05, 5-year survival rate 14% vs 53%, P<0.05) (Fig. 3). Since the familial group consisted of the probands and their affected relatives who were identified

by chance by familial screening, we also compared the prognosis of only the probands with that of patients in the non-familial group. Similar results were obtained: although there was no difference in the survival rate between the 2 groups (5-year survival rate 52% vs 64%, ns), when only NYHA class III and IV patients were selected, both the 1-year and 5-year survival rates were lower in the familial proband group than in the non-familial group (1-year survival rate 50% vs 84%, p<0.05, 5-year survival rate 20% vs 60%, p<0.05).

The causes of death were also investigated, and the deceased cases were divided into three categories: death due to congestive heart failure, sudden cardiac death, and death due to non-cardiac disease. In the non-familial IDC group, congestive heart failure was the most common cause of death. In the familial IDC group, however, sudden cardiac deaths were seen more frequently than deaths due to congestive heart failure (Fig. 4). Deaths due to congestive heart failure were seen in 71% of the deceased cases

(24 out of 34 cases) in the non-familial group, and in 45% (5 out of 11 cases) of those in the familial group ($p < 0.05$). On the other hand, sudden cardiac deaths were seen in only 21% (7 out of 34 cases) of the deceased cases in the non-familial group, while 55% (6 out of 11 cases) of the deceased cases in the familial group died of sudden cardiac death ($p < 0.05$). To investigate whether arrhythmia was related to sudden cardiac death, we compared the grade of Lown's classification. There was no significant difference in the grade of Lown's classification between familial sudden cardiac death patients and familial congestive heart failure death patients. There was also no significant difference in the grade of Lown's classification between familial sudden cardiac death patients and non-familial sudden cardiac death patients. However, the familial sudden cardiac death group tended to have a higher grade of Lown's classification than the other groups (familial sudden cardiac death group vs familial congestive heart failure death group vs non-familial sudden cardiac death group vs non-familial congestive heart failure death group; 4.2 ± 0.7 vs 3.6 ± 0.8 vs 3.7 ± 0.9 vs 3.7 ± 0.9 , ns respectively).

4. Comparison of Clinical Parameters in the Patients Who were Alive and the Deceased Patients of Familial Dilated Cardiomyopathy Group

To determine the characteristics of familial IDC patients who had a poor prognosis, we compared the clinical parameters at the time of diagnosis in patients who were alive to those in deceased patients in familial IDC families (Table III). The mean follow-up period was 2722 days in the patients alive and 635 days in the deceased patients ($p < 0.01$). The pulmonary capillary wedge pressure and the left ventricular end-diastolic pressure were significantly higher, and the cardiac index was significantly lower, in the deceased patients than in the patients alive. Fractional shortening tended to be lower, but not significantly. None of the other parameters showed any differences. Fifty-four percent of the patients alive were relatives (6 probands and 7 relatives), whereas 64% of the deceased patients were relatives (4 probands and 7 relatives). Thus, any differences

in hemodynamic parameters were not due to the presence of affected relatives who were identified by chance by family screening.

DISCUSSION

1. The Prevalence of Familial Dilated Cardiomyopathy Patients

In contrast to hypertrophic cardiomyopathy, familial aggregation of dilated cardiomyopathy has been considered to be rare. However, recent studies have shown several families with familial aggregation and have suggested that IDC is more frequently familial than has been generally recognized. Several investigators have reported that the familial aggregation of IDC ranges from 2 to 30%⁸⁻¹⁶. Recently, Michels et al¹⁶ investigated 59 families with 59 IDC probands and 315 relatives, and found familial aggregation in 12 families (20%).

In our study, familial IDC was suspected in 29 of 117 IDC families (25%). Ten of the 29 families (9% of the total) were "confirmed familial IDC families", and the remaining 19 (16%) were "suspected familial IDC families", in which there was not enough information to confirm the diagnosis. When suspected families are taken in account, the present value is similar to that in Michels'¹⁶ study. However, in contrast to hypertrophic cardiomyopathy, which shows a high familial aggregation ranging from 40% to 70%^{3,14,19,20} and in which most cases show autosomal dominant transmission,²⁰ the penetrance of familial IDC is quite incomplete,¹⁹ and the disease itself is multifactorial and diverse in character.¹ Moreover, the prognosis of patients with IDC is fairly poor and it is difficult to find several patients surviving in a single family at the same time. These factors help to explain why it is difficult to evaluate the prevalence of familial IDC. In both our study and Michels'¹⁶ study, the subjects were not chosen randomly, and only cooperative relatives were studied. Therefore, we cannot exclude the possibility that some of the family members who were not studied, may have been affected. Furthermore, some relatives may be in the latent stage of the disease, and may not have appeared in the family history. The wide differences in the prevalence reported by several investigators⁸⁻¹⁶ might be related

not only to different methodologies, but also to these survey problems. This is a limitation of studies of this type.

2. *Clinical Characteristics of Familial Dilated Cardiomyopathy Patients*

In this study, the age at the time of diagnosis in the familial group was lower than that in the non-familial group. This finding is similar to observations made by other investigators, such as Adachi et al⁵, Michels et al⁸, and Mestroni et al¹⁵. In addition, familial IDC patients tended to have milder symptoms, as reflected by NYHA classification. The milder symptoms and younger ages of the familial IDC patients might result from the fact that the familial group included affected relatives who were detected as part of the family screening process. However, we would like to emphasize that even though the familial IDC patients were younger and showed milder symptoms, there were no differences in the parameters of cardiac function between the two groups. These results suggest that the young age of presentation and the relatively few symptoms besides poor cardiac function, may be characteristic of the familial IDC patients, which may be one of the reasons why they do not limit their activities, and as a result delay visiting medical facilities. Therefore, we must consider the importance of family screening.

3. *Causes of Death in Familial Dilated Cardiomyopathy Patients*

MacLennan et al²¹ described a family with IDC, in which there were young affected members and a high incidence of sudden death. Yamaguchi and Toshima¹⁹ also reported a high incidence of young sudden death in the pedigree of familial IDC, in addition to the relatives studied.

In our investigation, sudden cardiac death was seen in 6 of 11 deceased familial IDC patients (55%), while congestive heart failure was the most common cause of death in non-familial IDC patients. Moreover, there were 6 additional sudden death members who were not studied in these 10 families. A high risk of young sudden death may be characteristic of familial-type IDC. This finding is consistent with those of previous investigations^{19,21}.

4. *Prognosis of Familial Dilated Cardiomyopathy Patients*

In general, familial IDC is believed to develop rapidly, and is an indication for cardiac transplantation. However, few studies have evaluated the prognosis of familial cases in detail^{5,7}. Adachi et al⁵ observed that 3 of 5 cases (60%) of familial IDC patients died within a year. In this study, we evaluated the prognosis of familial IDC patients using the Kaplan-Meier method. There was no difference in the overall survival rate between the familial group and the non-familial group. However, in patients with severe cardiac symptoms at the time of diagnosis (NYHA class III or IV), the 1-year and 5-year survival rates were significantly lower in familial IDC patients than in non-familial IDC patients. Moreover, in the familial group, cardiac function in the deceased patients was significantly worse than that in the patients who were alive. These findings suggest that once heart failure becomes severe in familial IDC, the disease progresses rapidly, and leads to cardiac death (sudden cardiac death or death due to congestive heart failure) despite full medication. This finding highlights the importance of early detection of familial cases by family study.

5. *The Pathogenetic Mechanism of Familial Dilated Cardiomyopathy*

Two major mechanisms are suspected in the development of familial cardiomyopathy¹⁵.

The first mechanism is that the myocardial damage itself is genetically determined. The second proposed mechanism is that impaired responses to predisposing factors, such as impaired immunoregulatory system²²⁻²⁵ are determined genetically. Regarding the first mechanism, the mutation of a β -cardiac myosin heavy chain gene has recently been reported in hypertrophic cardiomyopathy^{26,27}. Yazaki et al²⁸ reported a high incidence of fetal-type cardiac myosin expression in IDC. Abnormalities in the structure and genes of mitochondria have also been observed in IDC^{13,29-32}. However, since IDC is a disease with various aspects, the second mechanism is more likely. In particular, the relation of myocarditis and IDC³³⁻³⁸ to the alteration of immunoregulation^{7,22,39-41} has recently been emphasized,

and enteroviral genomes have been detected in the myocardium of IDC patients.^{38,42,43} Further studies, including gene mapping for familial IDC patients, must be undertaken in the future to investigate this mechanism and to improve the prognosis of such patients.

CONCLUSIONS

We conclude that a young age of presentation combined with mild symptoms, besides severe cardiac dysfunction, may be characteristic of familial IDC patients. Once their cardiac symptoms become severe, the disease progresses rapidly and leads to a poor prognosis. Therefore, early detection and early treatment appear to be indispensable for familial IDC patients.

REFERENCES

- Goodwin JF: The frontiers of cardiomyopathy. *Br Heart J* 1982; **48**: 1–18
- Johnson RA, Palacios I: Dilated cardiomyopathies of the adult. *N Engl J Med* 1982; **307**: 1051–1058
- Yamaguchi M, Toshima H, Yanase T: Genetic heterogeneity of idiopathic cardiomyopathy. *Jpn Circ J* 1978; **42**: 1131–1132
- Report of the WHO/ISFC task force on the definition and classification of cardiomyopathies. *Br Heart J* 1980; **44**: 672–673
- Adachi K, Ogata M, Tanaka H, Yamashita Y, Terasawa M, Toshima M, Koga Y: Factors related to the pathogenesis and clinicopathological findings in dilated cardiomyopathy. *J Cardiograph* 1986; **16**: 3–7
- Kawai S, Okada R: A histopathological study of dilated cardiomyopathy: With special reference to clinical and pathological comparisons of degeneration-predominant type and fibrosis-predominant type. *Jpn Circ J* 1987; **51**: 654–660
- Koga Y, Adachi K, Toshima H, Takamoto T, Yokoyama M: Dilated cardiomyopathy: Clinical significance of possible related factors. *Jpn Circ J* 1987; **51**: 689–698
- Michels VV, Driscoll DJ, Miller FA: Familial aggregation of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1985; **55**: 1232–1233
- Unverferth DV, Wooley CF: Familial dilated cardiomyopathy. In: Unverferth DV, editor. Dilated Cardiomyopathy. Mount Kisco, New York: Futura Publishing, 1985; 159–165
- Costanzo-Nordin MR, O'Connell JB, Engelmeier RS, Moran JF, Scanlon PJ: Dilated cardiomyopathy functional status, hemodynamics, arrhythmias, and prognosis. *Cathet Cardiovasc Diagn* 1985; **11**: 445–453
- Lengyel M, Kokeny M: Follow-up study in congestive (dilated) cardiomyopathy. *Acta Cardiol* 1981; **1**: 35–48
- Sekiguchi M, Hasegawa A, Ando M: A proposal for analyzing the familial occurrence of cardiomyopathy in the clinical situation. In: Sekiguchi M, Olsen EGJ, editors. Cardiomyopathy: Clinical, Pathological and Theoretical Aspects. Baltimore: University Park Press, 1980; 445–453
- Valantine HA, Hunt SA, Fowler MB, Billingham ME, Schroeder JS: Frequency of familial nature of dilated cardiomyopathy and usefulness of cardiac transplantation in this subset. *Am J Cardiol* 1989; **63**: 959–963
- Emanuel R, Withers R, O'Brien K: Dominant and recessive modes of inheritance in idiopathic cardiomyopathy. *Lancet* 1971; **2**: 1065–1067
- Mestroni L, Miani D, Di Lenarda A, Silvestri F, Bussani R, Filippi G, Camerini F: Clinical and pathologic study of familial dilated cardiomyopathy. *Am J Cardiol* 1990; **65**: 1449–1453
- Michels VV, Moll PP, Miller FA, Tajik AJ, Chu JS, Driscoll DJ, Burnett JC, Rodeheffer RJ, Chesebro JH, Tazelaar HD: The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. *N Engl J Med* 1992; **326**: 77–82
- Sahn DJ, DeMaria A, Kisslo J, Weyman A: Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 1978; **58**: 1072–1083
- Myebug M, Castellanos A: Cardiac arrest and sudden cardiac death. In: Braunwald E, editor. Heart Disease. Philadelphia: Saunders Publishing, 1988; 742–777
- Yamaguchi M, Toshima H: A genetic analysis of idiopathic cardiomyopathies in Japan. In: Sekiguchi M, Olsen EGJ, editors. Cardiomyopathy: Clinical, Pathological and Theoretical Aspects. Baltimore: University Park Press, 1980; 421–428
- Ando M, Takao A, Mori K, Sekiguchi M: The mode of inheritance in idiopathic cardiomyopathy: A preliminary report. In: Sekiguchi M, Olsen EGJ, editors. Cardiomyopathy: Clinical, Pathological and Theoretical Aspects. Baltimore: University Park Press, 1980; 429–444
- MacLennan BA, Tsoi EY, Maguire C, Adgey AAJ: Familial idiopathic congestive cardiomyopathy in three generations: A family study with eight affected members. *Q J Med* 1987; **63**: 335–347
- Yamakawa K, Fukuta S, Yoshinaga T, Umemoto S, Itagaki T, Kusakawa R: Study of immunological mechanism in dilated cardiomyopathy. *Jpn Circ J* 1987; **51**: 665–675
- Arbustini E, Gavazzi A, Pozzi R, Grasso M, Pucci A, Campana C, Graziano G, Martinetti M, Cuccia M, Salveneschi L, Martinelli L, Montemartini C, Viganò M: The morphologic spectrum of dilated cardiomyopathy and its relation to immune-response gene. *Am J Cardiol* 1989; **64**: 991–995
- Limas CJ, Limas C, Kubo SH, Olivari MT: Anti-beta receptor antibodies in human dilated cardiomyopathy and correlation with HLA-DR antigens. *Am J Cardiol* 1990; **65**: 483–487
- Anderson JL, Carlquist JF, Lutz LR, DeWitt CW, Hammond EH: HLA A, B and DR typing in idiopathic dilated cardiomyopathy: A search for immune response factors. *Am J Cardiol* 1984; **53**:

- 1326–1330
26. Tanigawa G, Jarcho JA, Kass S, Solomon S, Vosberg HP, Seidman JG, Seidman CE: A molecular basis for familial hypertrophic cardiomyopathy: An α/β cardiac myosin heavy chain hybrid gene. *Cell* 1990; **62**: 991–998
27. Anja AT, Lowrance G, Kass S, Tanigawa G, Vosberg HP, McKenna W, Seidman CE, Seidman JG: A molecular basis for familial hypertrophic cardiomyopathy: An β cardiac myosin heavy chain genemissense mutation. *Cell* 1990; **62**: 999–1006
28. Yazaki Y, Tsuchimoto H, Kurabayashi M, Kawana M, Kimata S: Distribution of cardiac myosin isozymes in cardiomyopathy: Immunohistochemical and gene analysis. *Jpn Circ J* 1987; **51**: 676–681
29. Urie PM, Billingham ME: Ultrastructural features of familial cardiomyopathy. *Am J Cardiol* 1988; **62**: 325–327
30. Ozawa T, Tanaka M, Sugiyama S, Hattori K, Ito T, Ohno K, Takahashi A, Sato W, Takada G, Mayumi B, Yamamoto K, Adachi K, Koga Y, Toshima H: Multiple mitochondrial DNA deletion exist in cardiomyocytes of patients with hypertrophic or dilated cardiomyopathy. *Biochem Biophys Res Commun* 1990; **170**: 830–836
31. Ito T, Hattori K, Obayashi T, Tanaka M, Sugiyama S, Ozawa T: Mitochondrial DNA mutations in cardiomyopathy. *Jpn Circ J* 1992; **56**: 1045–1053
32. Unverferth BJ, Leier CV, Magorien RD, Unverferth DV: Differentiating characteristics of myocardial nuclei in cardiomyopathy. *Hum Pathol* 1983; **14**: 974–983
33. O'Connell JB, Fowles RE, Robinson JA, Subramanian R, Henkin RE, Gunnar RM: Clinical and pathologic findings of myocarditis in two families with dilated cardiomyopathy. *Am Heart J* 1983; **107**: 127–135
34. Onishi S, Wada O: Heredofamilial factors as a cause of myocardial damage. *Heart Vessels* 1985; (Suppl 1): 34–38
35. Matsumori A, Kawai C, Crumpacker CS, Abelmann WH: Pathogenesis and preventive and therapeutic trials in an animal model of dilated cardiomyopathy induced by a virus. *Jpn Circ J* 1987; **51**: 661–664
36. Quigley PJ, Richardson PJ, Meany BT, Olsen EGJ, Monaghan MJ, Jackson G, Jewitt DE: Long-term follow-up of acute myocarditis: Correlation of ventricular function and outcome. *Eur Heart J* 1987; **8**(Suppl J): 39–42
37. Muir P, Nicholson F, Tilzey AJ, Signy M, English TAH, Banatvala JE: Chronic relapsing pericarditis and dilated cardiomyopathy: Serological evidence of persistent enterovirus infection. *Lancet* 1989; **1**: 804–807
38. Bowles NE, Richardson PJ, Olsen EGJ, Archard LC: Detection of Coxsackie-B-Virus specific RNA sequences in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopathy. *Lancet* 1986; **1**: 1120–1123
39. Nishi H, Kimura A, Fukuta S, Kusukawa R, Kawamura K, Nimura Y, Nagano M, Yasuda H, Kawai C, Sugimoto T, Okada R, Yazaki Y, Tanaka H, Harumi K, Koga Y, Sasazuki T, Toshima H: Genetic analysis of dilated cardiomyopathy: HLA and immunoglobulin genes may confer susceptibility. *Jpn Circ J* 1992; **56**: 1054–1061
40. Seko Y, Yamazaki T, Shinkai Y, Yagita H, Okumura K, Naito S, Imataka K, Fujii J, Yazaki Y: Cellular and molecular bases for the immunopathology of the myocardial cell damage involved in acute viral myocarditis with special reference to dilated cardiomyopathy. *Jpn Circ J* 1992; **56**: 1062–1072
41. Fukuta S, Yoshinaga T, Yamakawa K, Kimura Y, Kusukawa R: Dilated cardiomyopathy with special reference to humoral immunity. *Jpn Circ J* 1992; **56**: 1073–1080
42. Kandolf R: The impact of recombinant DNA technology on the study of enteroviral heart disease. In: Benclinelli M, Friedman H, editors. *Coxsackievirus-A General Update*. New York: Plenum Press, 1988; 293–318
43. Koide H, Kitaura Y, Deguchi H, Ukimura A, Kawamura K, Hirai K: Genomic detection of enteroviruses in the myocardium: Studies on animal hearts with coxsackievirus B3 myocarditis and endomyocardial biopsies from patients with myocarditis and dilated cardiomyopathy. *Jpn Circ J* 1992; **56**: 1081–1093