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Prevalence of hepatitis C virus infection among patients with hypertrophic cardiomyopathy

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Abstract Hypertrophic cardiomyopathy (HCM) is defined as inappropriate ventricular hypertrophy without a cardiac or systemic cause. On the other hand, hepatitis C virus (HCV) causes extrahepatic manifestations as well as chronic persistent infection in hepatocytes. We studied the association of HCV infection with HCM, comparing the prevalence of HCV antibodies between HCM patients and age- and gender-matched controls with other cardiovascular diseases at a single institution, for reasons of exclusion of bias. We then described the clinical features and genotype analysis of HCV RNA in HCM. The diagnosis of HCM was established by echocardiographic demonstration of a hypertrophied (≥15 mm), nondilated left ventricle in the absence of another systemic or cardiovascular disease capable of producing the magnitude of hypertrophy observed. The study population consisted of 80 patients with HCM, in whom HCV antibody was examined (55 men and 25 women; mean age 56.6 ± 12.4 years; ranging from 19 to 80 years), compared with a total of 80 age- and gender-matched controls without HCM. The prevalence of HCV infection in patients with HCM (18/80) was significantly higher than in control subjects (5/80) (χ^2 = 7.312, P = 0.007). Of the 12 patients in whom the genotype of HCV was analyzed, 7 had type 1b and 5 had type 2a. The prevalence of HCV infection was higher in patients with HCM than in age- and gender-matched control subjects with other cardiovascular diseases. The result suggests that HCV may play an important role in these HCV-positive HCM patients.

Key words Hepatitis C virus · Genotype analysis · Hypertrophic cardiomyopathy · Apical hypertrophy · Echocardiography

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Introduction

Hypertrophic cardiomyopathy (HCM) is defined as inappropriate ventricular hypertrophy without systemic or cardiac causes. Familial forms of HCM sometimes show several gene mutations, while sporadic, nonfamilial cases are often present and the cause remains unknown.

On the other hand, hepatitis C virus (HCV) causes extrahepatic lesions[1–8] as well as chronic persistent infection in hepatocytes. The prevalence of HCV in the general population is often wide-ranging because of geographical and age differences (0.5%–11.1%).[9–13] However, there have been few reports on the study of the prevalence of HCV in HCM patients which have appropriate control subjects.[14]

We investigated the association of HCV with HCM, comparing the prevalence of HCV antibodies between HCM patients and age- and gender-matched controls with other cardiovascular diseases at a single institution, for reasons of bias exclusion, and described the clinical features and genotype analysis of HCV RNA in HCM.

Materials and methods

Study population

We reviewed registries of the echocardiography laboratory at Osaka City University Hospital from April 1995 through March 2000. The WHO/ISFC criteria were used to define HCM.[15] Two-dimensional echocardiographic studies were available for 123 HCM patients. The diagnosis was estab-

Table 1. Underlying diseases in control subjects

Disease	*n*
Angina pectoris	35
Acute and old myocardial infarction	27
Atypical chest pain	4
Atrial septal defect	4
Valvular heart disease	4
Sick sinus syndrome	2
Others	4
Total	80

lished for each patient by echocardiographic demonstration of a hypertrophied, nondilated left ventricle in the absence of another systemic or cardiovascular disease capable of producing the same magnitude of hypertrophy. The magnitude and distribution of left ventricular hypertrophy was assessed in the parasternal short-axis plane, although parasternal long-axis and apical views were also used to integrate the information obtained from the short-axis image. M-mode echocardiograms were derived under direct anatomic visualization from two-dimensional images. A left ventricular wall more than 15 mm thick was judged hypertrophied.[16]

Antibodies against HCV were examined in 80 of 123 HCM patients (55 men, 25 women; mean age 56.6 ± 12.4 years; range, 19–80 years). These HCM patients were enrolled without knowledge of the results of their HCV examination. Informed consent was obtained from each patient in accordance with the Helsinki Declaration.

In contrast, a total of 80 patients without HCM, who had been admitted to our hospital from January 1993 through December 1999, served as age- and gender-matched controls without knowledge of the results of HCV antibodies. On admission, anti-HCV antibody had been examined in each patient. Exclusion criteria were: (1) left ventricular hypertrophy and/or dilatation, (2) history of coronary artery bypass surgery or valve surgery, and (3) hemodialysis and other diseases probably related to HCV infection.[1–8,17,18] The underlying diseases of the 80 control patients are shown in Table 1.

Laboratory analyses

Serum was stored at −80°C. HCV antibodies were analyzed with a third-generation enzyme-linked immunosorbent assay (Ortho Diagnostic Systems, Tokyo, Japan). HCV RNA was detected, as described previously, by nested reverse transcription–polymerase chain reaction with primers derived from a highly conserved 5′-untranslated region of the viral genome.[19] HCV RNA titer was measured by the Amplicor monitor method.

Statistical analyses

The difference in the prevalence of HCV antibodies in HCM patients and controls was assessed with Fisher's exact test. The test-based methods were used for 95% confidence

Table 2. Clinical features and analysis of HCV genomes

Case	Age (years)	Gender	Duration of disease (years)	Symptoms	NYHA	AST (IU/l)	ALT (IU/l)	Blood transfusion	HCV antibody	HCV genotype	RNA titer (kIU/ml)	Years after transfusion
1	48	M	13	SOB	I	33	26	−	+	1b	NA	
2	55	M	10	(ECG abnormality)	I	73	91	?	+	ND	ND	
3	56	M	4	POF	I	22	36	+	+	2a	>850	34
4	57	M	2	DOE	II	77	97	−	+	1b	152	
5	59	F	2	POF, DOE	II	45	25	+	+	ND	ND	49, 34
6	60	M	25	DOE	II	68	52	−	+	2a	8	
7	60	M	6	Palpitation	II	73	81	−	+	2a	11	
8	62	M	2	(ECG abnormality)	I	60	57	−	+	2a	159	
9	63	F	5	POF	II	55	68	+	+	ND	ND	44
10	63	F	–	(ECG abnormality)	I	41	16	−	+	1b	>850	
11	64	M	34	Palpitation	II	66	75	−	+	1b	>850	
12	65	M	10	Palpitation	II	161	168	−	+	ND	NA	
13	66	M	6	DOE, palpitation	II	34	57	+	+	NA	NA	8
14	67	F	5	Palpitation	II	29	28	+	+	2a	234	10
15	67	M	2	DOE	II	78	79	?	+	1b	NA	
16	77	M	7	DOE	II	37	18	?	+	ND	ND	
17	78	F	–	(ECG abnormality)	I	60	43	−	+	1b	48	
18	80	F	15	General fatigue	III	31	19	−	+	1b	304	

AST, asparatate aminotransferase (normal range: 12–40IU/l); ALT, alanine aminotransferase (normal range 10–45IU/l)
ND, not done; NA, not available; SOB, shortness of breath; POF, precordial oppressive feeling; DOE, dyspnea on exertion
ECG abnormality means that the abnormality was detected in a health checkup without any symptoms

Table 3. Electrocardiographic and echocardiographic data

Case	Electrocardiogram			Echocardiogram				
	R wave (mV)	SV1 + RV5 (mV)	T wave in V4 or V5 (mV)	IVS (mm)	PW (mm)	LVDd (mm)	LVDs (mm)	
1	0.3	2.4	−0.3	19	13	49	29	
2	4.1	6.3	−0.8	9	9	56	41	APH
3	3.4	4.8	−1.0	12	14	41	28	APH
4	2.5	5.7	−0.2	23	9	39	29	
5	3.1	5.1	−0.7	17	11	42	23	
6	2.5	4.3	−0.7	15	12	53	34	
7	4.5	10.7	−1.1	24	19	48	30	
8	5.0	7.1	1.1	15	13	44	21	
9	5.6	7.7	−0.8	18	12	38	20	
10	1.0	3.7	−1.2	17	11	42	30	
11	1.5	3.4	−0.3	10	10	59	48	
12	3.5	5.0	−0.5	14	19	42	20	
13	2.5	5.1	−0.4	19	11	42	20	
14	3.2	7.6	−0.7	23	12	44	30	
15	2.9	3.3	−1.2	9	9	49	29	APH
16	6.9	7.2	−1.6	12	12	53	37	APH
17	4.4	6.2	−0.4	18	10	49	29	
18	4.3	3.5	−0.7	8	9	61	36	APH

IVS, interventricular septum; PW, posterior wall of the left ventricle; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; APH, apical hypertrophy

intervals (95% CI) of the odds ratio.[20,21] The difference in the age between HCV-positive and -negative patients was compared using Student's *t*-test. A *P* value of less than 0.05 was considered statistically significant.

Results

During a 5-year period, 18 (22.5%) of the 80 HCM patients, in whom HCV antibody examination was performed, were confirmed as positive for HCV antibodies. In the 80 controls, only 5 (6.3%) were anti-HCV-positive. Therefore, HCV prevalence was significantly higher in the HCM patients than in controls ($\chi^2 = 7.31$, $P = 0.007$; odds ratio, 4.35; 95% CI, 1.11–17.11). Among the 80 HCM patients, the mean age in the 18 patients positive for HCV antibodies was significantly higher than in 62 patients who were negative (mean age 63.7 ± 8.2 years vs 54.5 ± 12.7 years, $P = 0.03$).

Table 2 shows the clinical characteristics and HCV genotype of the 18 patients with HCM and HCV infection. We analyzed the HCV RNA genotype in 13 of these patients. We detected type 1b in 7 and type 2a in 5 patients, excluding one patient without HCV RNA. Of these 18 patients, 5 (27.8%) showed characteristics of apical hypertrophy,[22,23] while 5 (8.1%) of the remaining 62 HCM patients were confirmed as well. Table 3 shows electrocardiographic and echocardiographic data of these 18 patients. Patient 11 suffered from the dilated form of HCM.

Discussion

This study suggests that the prevalence of HCV infection was significantly higher in HCM patients than in controls, after comparing the prevalence of HCV antibodies in HCM patients to that in age- and gender-matched control subjects at the same institution for similar periods. The prevalence of apical hypertrophy, moreover, was greater in patients with HCM and HCV infection than in those with HCM but without HCV infection.

In our study, geographical, age, and gender bias in controls was negligible. Our patients lived in and around the Osaka area and we enrolled age- and gender-matched controls. A Japanese epidemiological study showed the bias of HCV prevalence since the prevalence was greater in the Western area of Japan, mostly in males, and in older patients than in the Eastern area, where the patients were mainly female and younger.[11] Previous studies on the association of HCV with HCM used volunteer blood donors of the Japan Red Cross Blood Center as controls, whose age range was limited and narrower than HCM patients.[14,24,25] Hence, these should may have shown bias because the geographical difference of controls was not considered and the control subjects were not age- and gender-matched.

Our results showed that the prevalence of apical hypertrophy was greater in patients with HCM and HCV infection than in those with HCM but without HCV infection. A previous study also indicated a relationship between apical hypertrophy and HCV infection.[24]

Our study has a few limitations. We found no direct evidence of HCV infection in myocardial tissues in contrast to the results of other studies.[24,26] We had little data on the

relationship between subtypes of HCM and HCV infection, or linkage of clinical manifestations and HCV genotype. However, mitogen-activated protein kinase, which was activated by HCV core protein,[27] induced cardiac hypertrophy.[28]

We enrolled 80 HCM patients who had undergone HCV antibody examinations. However, even in a total of 123 HCM patients, the prevalence of HCV antibodies (18/123, 14.6%) was, at the lowest estimate, still significantly higher than prevalence in age- and gender-matched controls (7/123, 5.7%) ($\chi^2 = 5.39$, $P = 0.02$; odds ratio, 2.84; 95% CI, 1.18–6.86). Although further large-scale studies are required to clarify the mechanism from HCV infection to myocyte hypertrophy, this preliminary result suggests that HCV may play an important role in these HCV-positive HCM patients.

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