Elevated Serum Myosin Light Chain I in Influenza Patients

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Abstract

Objective **Myocarditis has been described as a complication of influenza. Patients with influenza may have symptoms and abnormal laboratory data (including chest X-ray, electrocardiogram, etc.) suggestive of myocarditis, although few observations have been made regarding the prevalence of asymptomatic myocardial injury. We investigated whether influenza can produce myocardial injury without cardiac symptoms.**

Methods **During the epidemic of influenza A (H3N2) from 1998 to 1999 in Japan, we examined possible cardiac muscle damage associated with influenza in patients without apparent clinical myocardial injury by measuring serum myosin light chain concentrations.**

Patients **Ninety-six influenza-positive patients (46 males and 50 females, average age 43.4 years) without impaired renal function were studied.**

Results **Of these patients, 11 (11.4%) had elevated serum myosin light chain I concentrations.**

Conclusion **Asymptomatic myocardial injury may be present in patients with influenza even when they have no symptoms suggestive of myocardial injury.**
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Key words: viral myocarditis, complications, myocardial injury, myocardiopathy, elderly people

Introduction

Pneumonia is a well-known complication of influenza. Other complications, including myocarditis, have been reported. Although Coxsackie virus is the most prominent causative agent of viral myocarditis, other respiratory viruses can also cause myocarditis with less frequency (1). The first two patients with influenza myocarditis were reported by Finland et al in 1945 (2). Myocarditis as a complication of influenza has been observed frequently since the Asian influenza epidemic of 1957 (3–5), although few studies have analyzed the prevalence of asymptomatic myocardial injury. It has been noted however, that elderly people, without apparent symptoms of myocarditis, may develop heart failure during the clinical course of influenza. We studied the influence of influenza virus infection on cardiac muscle by determining serum myosin light chain I (MLC I), a marker for myocardial injury.

Subjects and Methods

Subjects

Ninety-six influenza patients (46 males and 50 females, average age 43.4 years) without impaired renal function (serum creatinine level <1.1 mg/dl in males, <0.7 mg/dl in females) were studied from December 1998 to March 1999, during the influenza A (H3N2) epidemic. Informed consent was obtained from all patients prior to enrollment in the study.

Clinical and laboratory tests

Physical examinations were carried out at the first visit and at follow-up visits for the illness. Patients' blood samples were collected within 5 days after onset, and convalescent blood samples were collected about 1 month after the onset of illness. White blood cell count and serum concentrations of MLC I, asparate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), C-reactive protein (CRP), and creatine kinase (CK) were examined. All patients with abnormally high concentrations of MLC I and creatine kinase were followed until these values returned to normal. Serum MLC I concentrations were measured by radioimmunoassay (6).

Virologic examinations

Throat swabs from patients in the acute phase of illness were examined using an influenza rapid diagnosis system, Directigen Flu A (Becton Dickinson Microbiology Systems, Cockeysville, MD) (7, 8).

Serologic examination

Acute and convalescent sera were collected from all patients and stored at –70°C until a hemagglutination inhibition test was performed. A ≥4-fold increase in HI titer in the convalescent serum was considered positive. Data were analyzed statistically using Stat View software (Abacus Concepts, Berke-

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ley, CA). For continuous variables, the unpaired *t* test was used to assess the significance of differences between two groups. P values <0.05 were considered statistically significant.

Results

All 96 patients were positive for influenza A virus (H3N2). On physical examination, they showed no symptoms such as cardiomegaly, rale, gallop rhythm, or edema which suggest the presence of heart failure. Eleven patients (4 males and 7 females) had elevated serum MLC I concentrations, and the other 85 patients (42 males and 43 females) were within the normal range. For comparison the patients were divided into two groups, those with a high MLC I concentration and those with a normal MLC I concentration (Table 1). The presence of fever and other clinical symptoms was not significantly different between the groups. The day of the first visit to our clinic after the onset of symptoms and the data from the clinical examination are shown in Table 2. There were no differences in the two groups with regard to the number of days after onset of symp-

Table 1. Serum MLC I Concentration and Clinical Symptoms

Group	Number of patients	Main symptoms	Number of patients (% of total patients)		
			Chest pain	Dyspnea followed by cough	Myalgia
High MLC I group (MLC I ≧2.5 ng/ml)	11	Fever (100%) Headache (64%)	0 (0%)	1 (9%)	2 (18.1%)
Normal MLC I group (MLC I <2.5 ng/ml)	85	Fever (92%) Chill (72%)	9 (10.5%)	4 (4.7%)	15 (17.6%)

MLC I: myosin light chain I.

Table 2. Patient Characteristics and Serum Biochemical Parameters

Variables I	High MLC I group (MLC ≧2.5 ng/ml)	Normal MLC I group (MLC <2.5 ng/ml)	p
Age (years)	62±12	41±8**	0.004
Gender (M/F)	4/7	42/43	NS
Number of days after onset at presentation	2.5±0.3	3.2±0.8	NS
Body temperature (°C)	38.0±0.7	37.7±0.8	0.042
CRP (mg/dl)	2.1±0.5	3.1±0.9	NS
WBC (/mm^3)	5,682±499	6,075±303	NS
Creatine kinase (IU/l/37°C)	357±202	145±25	0.032
MLC I (ng/ml)	9.4±2	1.2±0.08	0.0001

**mean±S.D. NS: not significant, CRP: C-reactive protein, WBC: white blood cell, MLC I: myosin light chain I.

Table 3. Clinical Data of 11 Cases with High MLC I

Case	Gender /age	Temp (°C)	CRP (mg/dl)	WBC (/mm³)	AST (IU//37°C)	ALT (IU//37°C)	LDH (IU//37°C)	CRE (mg/dl)
1	F/89	38.1	2	6,810	15	22	185	0.8
2	M/41	38.2	0.6	4,830	22	19	265	0.7
3	M/70	37.0	1	5,180	38	34	304	0.7
4	F/66	36.9	2	6,140	16	21	398	1.0
5	F/64	37.0	0.7	5,800	18	18	250	1.1
6	F/18	39.4	2.3	4,890	22	23	454	0.9
7	F/84	38.2	5.5	9,750	16	19	400	0.7
8	F/58	39.5	1.5	6,000	20	19	251	1.0
9	M/86	38.0	0.9	3,200	20	39	148	0.6
10	F/72	38.0	2.8	5,430	26	24	35	0.9
11	M/64	38.0	3.7	4,480	40	58	520	0.6

Case	CK		CK-MB (ng/ml)	MLC I	
	Acute (IU//37°C)	Convalescent (IU//37°C)		Acute (ng/ml)	Convalescent (ng/ml)
1	220	132	<5	3.0	<1
2	159	–	<5	4.3	–
3	71	120	<5	4.5	<1
4	161	158	<5	4.6	1.2
5	124	130	<5	5.4	<1
6	50	120	7	7.1	1
7	114	–	<5	8.0	–
8	99	145	7	9.1	<1
9	164	255	10	17.0	<1
10	408	368	10	20.0	1.3
11	2364	102	20	21.0	2.5

Temp: body temperature, CRP: C-reactive protein, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CRE: creatinine, CK: creatine kinase, CK-MB: creatine kinase isoenzyme, MLC I: myosin light chain I. Normal values: CRP <1.0, WBC <9,000, AST 13–33, ALT 5–40, LDH 230–460, CRE male 0.6–1.1/female 0.4–0.7, CK male 57–197/female 32–180, CK-MB <5, MLC I <1.

toms at presentation, C-reactive protein, or white blood cell counts. However, body temperature, creatine kinase, and age differed significantly between the two groups.

The clinical features of 11 patients with elevated MLC I concentrations are shown in Table 3. Five patients had elevated CK-MB (creatine kinase MB isozyme) concentrations. One patient had an abnormal serum concentration of lactate dehydrogenase, which likely originated from skeletal muscle, and 3 patients (27.2%) had elevated creatine phosphokinase concentrations, which also were probably from skeletal muscle. One patient sustained an abnormal concentration of MLC I in the convalescent phase. All other abnormal values returned to normal. No patient in this study had abnormal findings on chest radiogram, echocardiogram, or electrocardiogram.

Discussion

Recently, the number of case reports of myocarditis in patients with influenza has been increasing. Influenza virus is an important causative agent of viral myocarditis (9, 10). We measured serum MLC I concentration, which is a sensitive indicator of myocardial injury. We did not consider the MLC I elevation in the present 11 patients to be direct evidence of myocarditis. However, the presence of MLC I in serum suggested that myocardial injury had occurred even in the patients with a normal serum creatine kinase concentration. The amount of MLC I present in the serum reflects the degree of damage to cardiac myocytes. This protein is not influenced by circadian rhythm or physical exercise. As MLC I may also be elevated in patients with severe skeletal muscle damage, creatine phos-

phokinase, which is also an indicator of skeletal muscle damage, was additionally measured and it was within the normal range. Furthermore no clinical symptoms such as extremital myalgia and muscle weakness which suggest skeletal muscle damage were observed. It has been shown that patients with renal failure may have abnormal concentrations of MLC I; therefore, we excluded patients with impaired renal function from this study. Thus the data obtained in the present study strongly suggest that the elevated MLC I was of cardiac origin. It was concluded that myocardial injury may occur in patients with influenza even when no symptoms, including chest pain and dyspnea caused by the continuance of severe coughs and no abnormal electrocardiogram or chest radiogram are present.

Myocardial injury may be an important new cardiac complication of influenza. And when elderly people are infected by influenza, it is critical to carefully treat the complications of asymptomatic myocardial injury as well as pneumonia.

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