Clinical Microbiology: Open Access
ISSN: 2327-5073

Ukimura et al., Clin Microbial 2014, 3:2
DOI: 10.4172/2327-5073.1000143

Research Article Open Access

National Survey of Influenza Myocarditis in Japanese Children in Three Seasons

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Abstract

An Influenza pandemic occurred in 2009. A nationwide, retrospective survey of Influenza myocarditis in Japanese children in 3 consecutive Influenza seasons was performed to compare Influenza myocarditis in the 2009/2010 season (the pandemic season), the 2010/2011 season, and the 2011/2012 season, by mailing questionnaires to 514 hospitals in Japan that have pediatric departments and collecting data from 285 hospitals. A questionnaire-based survey related to Influenza myocarditis was also conducted to evaluate the attitudes of Japanese pediatricians concerning the diagnosis of Influenza myocarditis. Fifteen Influenza myocarditis patients were reported, with 8 (H1N1pdm:6, type A:1, type B:1) from the 2009/10 season, 4 (type A:1, type B:3) from the 2010/11 season, and 3 (type B:3) from the 2011/12 season. Only 8 patients with Influenza A virus myocarditis were reported, with 7 patients from the 2009/2010 season, one from the 2010/2011 season, and none in the 2011/2012 season. Mortality was 33.3% (5/15) among the myocarditis patients. Twelve patients (12/15, 80%) were diagnosed with fulminant myocarditis with fatal arrhythmias and/or cardiogenic shock. In the pediatricians' attitude survey, only 3.3% of pediatricians routinely examined the electrocardiograms of children hospitalized with Influenza infection in Japan. The number of Japanese children with myocarditis associated with Influenza A virus seemed to increase in the pandemic season. Increased awareness of Influenza myocarditis in children is needed during future Influenza pandemics.

Keywords: Myocarditis; Influenza; Pandemic; Cardiogenic shock

Introduction

Acute myocarditis is a potentially lethal disease, and the etiological agents of viral myocarditis include Enteroviruses, Adenoviruses, Parvoviruses, Cytomegalovirus, Influenza virus and others [1-10]. Fulminant myocarditis causes severe hemodynamic dysfunction and requires high-dose catecholamine and mechanical circulatory support [1,6-8,11]. An Influenza pandemic occurred in 2009 [6,12-14]. The causative organism, Influenza H1N1pdm, has been reported to cause fatal myocarditis as well as pneumonia [2-4,6-10]. Based on national surveillance in Japan, we previously reported that fifteen fulminant myocarditis patients (adults: 13, children: 2) with Influenza A H1N1pdm were seen in the 2009/2010 season, while only two (adults: 2, children: 0) were seen in the 2010/2011 season, and that electrocardiogram (ECG) was useful for screening for myocarditis [7].

Patients and Methods

A nationwide, retrospective survey of Influenza myocarditis in Japanese children in 3 consecutive Influenza seasons was performed to compare Influenza myocarditis in the 2009/2010 season (the pandemic season), the 2010/2011 season, and the 2011/2012 season by mailing questionnaires to 514 hospitals in Japan that have pediatric departments. A fill-in-the-blanks and multiple-choice questionnaire was designed to obtain information on patient profiles, laboratory findings, treatment, outcomes and other data. Myocarditis was diagnosed using the Guidelines for Diagnosis and Treatment of Myocarditis (JCS 2009). The presence of compatible clinical symptoms, echocardiographic abnormalities in the absence of cardiac ischemia, leakage of cardiac enzymes and/or other evidence of myocardial damage suggested that a diagnosis of myocarditis was highly probable. Laboratory diagnosis of Influenza was made by quick Influenza diagnostic testing or probe-based real-time polymerase chain reaction (RT-PCR) using a nasopharyngeal swab or sputum, or viral titer elevation. A questionnaire-based survey related to Influenza myocarditis was performed to evaluate the attitudes of Japanese pediatricians concerning the diagnosis of Influenza myocarditis. The study protocol was approved by the Institutional Review Board of Osaka Medical College.

Results

Completed questionnaires were received from 285 hospitals that have pediatric departments in Japan. About 300,000 children were admitted per year in these hospitals. Fifteen Influenza myocarditis patients were reported, with 8 (H1N1pdm2009:6, type A:1, type B:1) from the 2009/2010 season, 4 (type A:1, type B:3) from the 2010/2011 season, and 3 (type B:3) from the 2011/2012 season (Table 1). Only 8 patients with Influenza A virus myocarditis were reported, with 7 patients from the 2009/2010 season, only one from the 2010/2011 season, and none in the 2011/2012 season (H3N2 dominant season). Cardiac symptoms developed on the first to third day of illness in most patients. Mortality was 33.3% (5/15) among the myocarditis patients. Twelve patients (12/15, 80%) were diagnosed with fulminant myocarditis with fatal arrhythmias and/or cardiogenic shock. Myocardial circulatory support was emergently inserted in 4 patients, three of whom were rescued. Three of the 9 patients treated without myocardial circulatory support survived. Respirators were used in 9 patients. Myocardial biopsies were not performed, and autopsy showed myocarditis in two patients.

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Received February 21, 2014; **Accepted** April 15, 2014; **Published** April 20, 2014

Citation: Ukimura A, Kishi K, Yamada T, Shibata Y, Ooi Y, et al. (2014) National Survey of Influenza Myocarditis in Japanese Children in Three Seasons. Clin Microbial 3: 143. doi:10.4172/2327-5073.1000143

Characteristics of paediatric myocarditis patients associated with influenza virus in 3 seasons in Japan														
Season/ Patient No.	Age/ sex	Baseline Disease	Card iac symptom/ onset (day post symptoms of influenza)	Type of myocarditis	Pneumonia or Enchepalopathy	RT-PCR or rapid diagnostic testing	ECG findings	Echocardiographic findings	Peak of Cardiac Enzyme	Medical treatment	Ventilator	Mechanical Support	Biopsy or Autopsy	Outcome
2009-2010/1	5/M	none	no information	fulminant myocarditis	no information	2009A (H1N1)	no information	no information	no information	oseltamivir	used	not used	not done	Death
2009-2010/2	6/M	asthma	dyspnea/day 3	fulminant myocarditis	pneumonia	2009A (H1N1)	VF,T inversion	diffuse hypokinesis EF33%	CPK 25,224	oseltamivir	used	PCPS	not done	Improved
2009-2010/3	11/F	none	shock/day 3	fulminant myocarditis	none	2009A (H1N1)	low voltage ST elevation	diffuse hypokinesisedema of LV wall	CK-MB918	oseltamivir steroid g-globulin	used	PCPS IABP	not done	Improved
2009-2010/4	12/M	brain tumor	consciousness disturbance/ day 1	fulminant myocarditi	pneumonia	2009A (H1N1)	low voltage T inversion	diffuse hypokinesis	no information	steroid g-globulin	used	not used	not done	Death
2009-2010/5	15/M	none	chest pain/day 2	acute myocarditis,	none	elevation of HI titer (Influenza A)	ST elevation	pericardial effusion	CPK 304 CK-MB 56	conservative therapy	not used	not used	not done	Improved
2009-2010/6	7/M	none	chest pain/day 2	fulminant myocarditis	none	2009A (H1N1)	sinus tachycardia low voltage	hypokinesis with pericardial effusion	CPK 5,163 CK-MB 128	oseltamivir, g-globulin	used	not used	not done	Improved
2009-2010/7	14/F	none	dyspnea/day 3	fulminant myocarditis	none	2009A (H1N1)	T inversion	pericardial effusion	no information	conservative therapy	not used	not used	Autopsy mild myocarditis	Death
2009-2010/8	8/F	epilepsy	dyspnea, chest pain/ day 4	acute myocarditis	none	B positive by rapid test	T inversion	hypokinesis with pericardial effusion	CPK 1933 CK-MB 33	g-globulin	not used	not used	not done	Improved
2010-2011/1	1/F	none	shock/ day 6	fulminant myocarditis	none	A positive by rapid test	ST elevation	diffuse hypokinesis EF20%	CPK 21,818	oseltamivir, g-globulin	used	not used	not done	Incomplete improvement
2010-2011/2	7/F	none	consciounsness disturbance / day 8	fulminant myocarditis	none	B positive by rapid test	low voltage ST elevation	diffuse hypokinesis pericardial effusion	CPK 7,091 CK-MB 175	oseltamivir, g-globulin steroid	used	not used	not done	Improved
2010-2011/3	5/F	asthma	abdominal pain/ day 3	fulminant myocarditis	none	B positive by rapid test	no information	no information	CPK elevation	zanamivir	not used	not used	Autopsy myocarditis	Death
2010-2011/4	11/F	none	dyspnea/ day 5	fulminant myocarditis	none	B positive by rapid test	ST elevation	diffuse hypokinesis	CPK 37,979 CK-MB 583	peramivir g-globulin	used	PCPS	not done	Improved
2011-2012/1	8/F	none	dyspnea/ day 3	fulminant myocarditis	enchepalopathy pneumonia	B positive by rapid test	low voltage ST elevation	diffuse hypokinesis	CPK elevation	peramivir steroid g-globulin	not used	not used	not done	Improved
2011-2012/2	6/M	T/F s/p OP	shock/day 3	fulminant myocarditis	encepalopathy	B positive by rapid test	T inversion	diffuse hypokinesis	CPK 736	oseltamivir	used	PCPS	not done	Death
2011-2012/3	10/F	none	dyspnea day 2	acute myocarditis	none	B positive by rapid test	ST elevation	pericardial effusion edema of LV wall	CPK 13,529 CK-MB 277	peramivir steroid g-globulin	not used	not used	not done	Improved

Table 1: Characteristics of pediatric myocarditis patients with influenza virus in 3 consecutive seasons in Japan
T/F s/p OP: following surgery for tetralogy of Fallot, RT-PCR: real-time polymerase chain reaction, HI: hemagglutination inhibition, VF: ventricular fibrillation, CPK: creatine phosphokinase, CK-MB: creatine kinase-MB, IABP: intra-aortic balloon pumping, PCPS: percutaneous cardiopulmonary support.

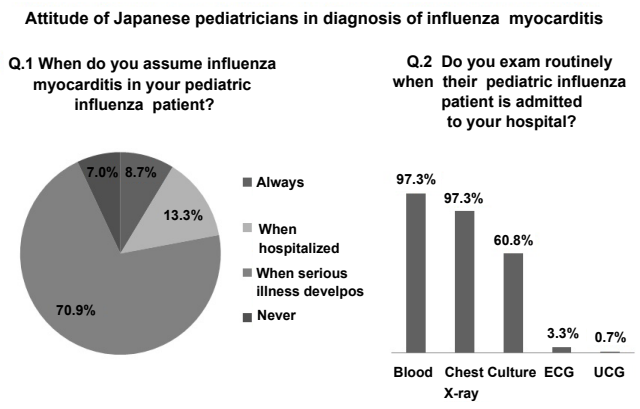

Figure 1: Attitudes of Japanese pediatricians to the diagnosis of influenza myocarditis
Question 1
When do you assume that your pediatric influenza patient may have influenza myocarditis?
Question 2
Which of the following do you examine routinely when your pediatric influenza patient is admitted to hospital?
ECG: Electrocardiogram, UCG: Ultrasound cardiogram

Ten patients had no baseline disease, and only two patients suffered from bronchial asthma. Three patients with myocarditis also developed pneumonia. RT-PCR or quick diagnostic testing yielded positive results in all patients. Most patients showed ECG abnormalities, such as ST segment elevation and/or T wave abnormality (ST-T abnormalities). Echocardiography revealed abnormalities of left ventricular wall motion in 10 patients. Cardiac dysfunction recovered almost completely in 9 patients, but partially remained in one patient. Eleven patients (73%) were treated with neuraminidase inhibitors.

Answers to the attitude survey concerning the diagnosis of Influenza myocarditis were received from 451 pediatricians (Figure 1). Overall, 8.4% of Japanese pediatricians always assumed the presence of Influenza myocarditis in pediatric Influenza patients, 13.2% in hospitalized patients, and 71.3% in patients with serious illness; however, 7.1% of Japanese pediatricians never assumed that Influenza myocarditis was present in pediatric Influenza patients. In addition, 87.6% of Japanese pediatricians routinely examined the chest X-rays when their pediatric patients were admitted to hospital, and 3.3% of pediatricians routinely examined the ECG, which is useful for screening of myocarditis (Figure 1).

Discussion

The Ministry of Health, Labor and Welfare of Japan confirmed only 198 deaths among about 20.61 million patients infected with Influenza A H1N1pdm in the 2009/2010 season, and 150 deaths among about 10.3 million patients in the 2010/2011 season in Japan [14]. The low case-fatality rate in Japan may be a result of early diagnosis and aggressive early intervention with antiviral drugs [15,16]. Twenty-five Influenza H1N1pdm myocarditis patients were reported in the 2009/2010 season, although only 4 were documented in the 2010/2011 season, and only 4

pediatric myocarditis patients were reported in 2 seasons in our previous study [7]. Since the number of pediatric myocarditis patients seemed to be smaller than in adult patients, this study was performed. Only 8 myocarditis patients with Influenza A virus were reported, with 7 from the 2009/2010 season, only one from the 2010/2011 season, and none in the 2011/2012 season in this study. The number of Japanese children with myocarditis associated with Influenza A virus seemed to increase in the pandemic season. A high prevalence of fulminant myocarditis was observed among the pediatric patients with myocarditis (12/15, 80%). Since cardiac symptoms developed on the first to third day of sickness in most pediatric myocarditis patients, and cardiac dysfunction progressed rapidly, early diagnosis and prompt treatment of acute myocarditis with heart failure are required in patients with Influenza infection during the pandemic season [6-10]. Appropriate intervention in patients with fulminant Influenza myocarditis consists of treatment with neuraminidase inhibitors to eliminate the causative virus, and mechanical circulatory support with intra-aortic balloon pumping or percutaneous cardiopulmonary support is very helpful for treating the depressed myocardial function [1,6-11,15,16] .

Myocarditis was proven by autopsy in only 2 fulminant myocarditis patients in this study, and the pathological findings were relatively mild. Many kinds of viruses have been implicated as a cause of myocarditis, with different viruses having different potentials to cause myocarditis [1-8]. The affinity of the Influenza virus for cardiac myocytes seemed to be low in previous studies [1-3,17,18]. The pathological mechanism of Influenza myocarditis appears to differ depending on the pathogen, and it may depend on host immunity. These results suggest that vaccination is able to suppress myocarditis associated with seasonal Influenza A virus in Japan.

The questions about the attitudes of Japanese pediatricians to the diagnosis of Influenza myocarditis showed that most of them did not usually assume that their patients had Influenza myocarditis. The ECG was found to be a sensitive and convenient tool for diagnosis of myocarditis in our previous study. ST elevation, T inversion, and conduction block are frequently observed. However, only 3.3% of Japanese pediatricians ordered routine ECGs on admission for Influenza. Thus, mild cases of myocarditis in children may be missed by pediatricians.

Conclusion

Increased awareness of Influenza myocarditis in children is very important during future Influenza pandemics.

Acknowledgement

This study was supported in part by a research grant for intractable diseases from the Ministry of Health, Labor and Walfare, and a grant for scientific research from the Ministry of Education, Science and Culture, Tokyo, Japan. The authors greatly appreciate the excellent assistance of Ms. T. Takabayashi.

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