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:8, 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 (ICS 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 (H1N1pdm:8, 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, 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. 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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Table 1: Characteristics of pediatric myocarditis patients associated with influenza virus in 3 consecutive seasons in Japan

| Season/Year | Age Sex | Baseline Disease | Type of myocarditis | Pneumonia or Encephalopathy | RT-PCR or rapid diagnostic testing | ECG findings | Echocardiographic findings | Peak of Cardiac Enzyme | Medical treatment | Ventilator | Mechanical Support | Bypass or Autopsy | Outcome |
|-------------|---------|------------------|---------------------|-----------------------------|----------------------------------|-------------|--------------------------|----------------------|----------------|-----------|----------------|----------------|---------|---------|
| 2009-2010/1| 5/M     | none             | 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           | fulminant myocarditis | pneumonia                  | 2009A (H1N1)                  | V, T inversion  | diffuse hypokinesia EF3% | CPK 25,224           | oseltamivir    | used      | PCPS              | not done       | Improved |
| 2011-2012/3| 9/F     | none             | fulminant myocarditis | low voltage ST elevation   | 2009A (H1N1)                  | low voltage T I  | diffuse hypokinesia      | CK-MB918            | oseltamivir    | used      | PCPS IABP        | not done       | Improved |
| 2012-2013/4| 12/M    | brain tumor      | consciousness disturban/ | day 1                       | 2009A (H1N1)                  | no information   | no information           | no information       | not used      | not used         | not used       | Death   |
| 2010-2011/5| 15/M    | none             | chest pain/day/2      | acute myocarditis           | none                           | elevation of HI titer (Influenza A) | ST elevation pericardial effusion | CPK 304 (intra-aortic balloon pumping) | not used      | not used         | not used       | Improved |
| 2012-2013/5| 7/M     | none             | chest pain/day/2      | acute myocarditis           | none                           | sinus tachycardia low voltage | hypokinesia with pericardial effusion | CPK 5,163 (CK-MB 128) | used          | not used         | not used       | Improved |
| 2010-2011/7| 14/F    | dyspnea day 7    | fulminant myocarditis | none                        | 2009A (H1N1)                  | T inversion      | no information           | no information       | conservative therapy | not used      | not used         | not done       | Improved |
| 2010-2011/8| 8/F     | epilepsy         | dyspnea, chest pain/4 | acute myocarditis           | none                           | B positive by rapid test | T inversion   | hypokinesia with pericardial effusion | CPK 1933 (CK-MB 33) | g-globulin     | not used         | not used       | Improved |
| 2011-2012/1| 1/F     | shock/ day 6     | fulminant myocarditis | none                        | A positive by rapid test       | ST elevation     | diffuse hypokinesia EF20% | CPK 21,818           | oseltamivir    | used          | not used         | not done       | Improved |
| 2010-2011/2| 7/F     | consciousness/ disturbance / day 6 | fulminant myocarditis | none                        | B positive by rapid test       | low voltage ST elevation | diffuse hypokinesia pericardial effusion | CPK 7,591 (CK-MB 175) | oseltamivir g-globulin | not 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 | CPK elevation            | zanamivir         | not used      | not used         | not done       | Death   |
| 2010-2011/4| 11/F    | dyspnea/ day 5   | fulminant myocarditis | none                        | B positive by rapid test       | ST elevation     | diffuse hypokinesia      | CPK 37,979 (CK-MB 583) | peramivir      | g-globulin     | used          | PCPS          | not done       | Improved |
| 2011-2012/1| 8/F     | dyspnea/ day 5   | fulminant myocarditis | none                        | B positive by rapid test       | low voltage ST elevation | diffuse hypokinesia      | CPK elevation            | peramivir      | g-globulin     | not used      | not used         | not done       | Improved |
| 2011-2012/2| 6/M     | T/F s/p OP       | shock/day 3           | fulminant myocarditis       | none                           | B positive by rapid test | T inversion    | diffuse hypokinesia      | CPK 736          | oseltamivir    | used          | PCPS          | not done       | Death   |
| 2011-2012/3| 10/F    | dyspnea day 2    | acute myocarditis     | none                        | B positive by rapid test       | ST elevation     | pericardial effusion edema of LV wall | CPK 13,029 (CK-MB 277) | peramivir      | 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


Figure 1: Attitudes of Japanese pediatricians to the diagnosis of influenza myocarditis

- **Q.1 When do you assume influenza myocarditis in your pediatric influenza patient?**
  - Always: 7.6%, When: 8.7%, Somatic illness: 13.3%, Never: 70.9%

- **Q.2 Do you examine routinely when your pediatric influenza patient is admitted to your hospital?**
  - Blood: 97.3%, Chest: 60.8%, Culture: 3.3%, ECG: 0.7%, UCG: 0.7%

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.

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References