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, 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 (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, 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 paediatric myocarditis patients associated with influenza virus in 3 consecutive seasons in Japan

| Season/Year | Patient No. | Age | Sex | Baseline Disease | Type of myocarditis | Pneumonia or Encephalopathy | RT-PCR or rapid diagnostic testing | ECG findings | Peak of Cardiac Enzyme | Medical Treatment | Mechanical Support | Biopsy or Autopsy | Outcomes |
|-------------|-------------|-----|-----|------------------|---------------------|-----------------------------|---------------------------------|-------------|----------------------|-----------------|------------------|---------------------|----------|
| 2009/2010/1 | 5/M         | 6   | M   | none             | fulminant myocarditis | no information             | no information                  | no information | no information       | Oseltamivir       | Used             | Not used           | Not done |
| 2009/2010/2 | 6/M         | 8   | M   | Asthma           | fulminant myocarditis | no information             | no information                  | no information | no information       | Oseltamivir       | Not used         | PCPS               | Improved |
| 2009/2010/3 | 11/F        | 4   | F   | Shock            | fulminant myocarditis | no information             | low voltage ST elevation         | diffuse hypokinesismetabolism of LV wall | CK-MB 918 | Oseltamivir           | Steroid          | G-globulin       | Not used           | Improved |
| 2009/2010/4 | 12/M        | 6   | M   | Brain tumor      | fulminant myocarditis | no information             | low voltage T inversion           | diffuse hypokinesis               | no information | Steroid             | G-globulin       | Not used         | Not used           | Death    |
| 2009/2010/5 | 15/M        | 8   | M   | Chest pain/day 2 | Acute myocarditis     | Acute myocarditis          | ST elevation                     | Pericardial effusion              | CPK 304       | Oseltamivir          | Conservative therapy | Not used         | Not used           | Improved |
| 2009/2010/6 | 7/M         | 10  | F   | None             | Acute myocarditis     | no information             | no information                  | CPK 5.163                | Oseltamivir          | G-globulin       | Not used         | Not used           | Improved |
| 2009/2010/7 | 14/F        | 6   | F   | Dyspnea/day 7   | Acute myocarditis     | Acute myocarditis          | no information                  | Pericardial effusion              | CPK 21.181             | Oseltamivir          | G-globulin       | Not used         | Not used           | Improved |
| 2009/2010/8 | 8/F         | 4   | F   | Epilepsy         | Acute myocarditis     | Acute myocarditis          | B positive by rapid test         | Hypokinesis with pericardial effusion | CPK 1933            | Oseltamivir          | G-globulin       | Not used         | Not used           | Improved |
| 2010/2011/1 | 1/F         | 6   | M   | Shock            | Acute myocarditis     | Acute myocarditis          | A positive by rapid test         | Hypokinesis with pericardial effusion | CPK 25.224             | Oseltamivir          | G-globulin       | Not used         | Not used           | Improved |
| 2010/2011/2 | 7/F         | 3   | F   | Consciousness disturbance/ Day 6 | Acute myocarditis | Acute myocarditis          | B positive by rapid test         | Low voltage ST elevation          | Pericardial effusion with hypokinesis of LV wall | CPK 7.591            | Oseltamivir          | G-globulin       | Not used         | Not used           | Improved |
| 2010/2011/3 | 5/F         | 4   | M   | Abdominal pain/day 3 | Acute myocarditis | Acute myocarditis          | No information                  | No information                  | CPK 57.979                | Peramivir           | G-globulin       | Not used         | PCPS              | Improved |
| 2010/2011/4 | 11/F        | 6   | M   | Dyspnea/day 1   | Acute myocarditis     | Acute myocarditis          | B positive by rapid test         | Hypokinesis              | CPK 37,979              | G-globulin       | Not used         | Not used           | Improved |
| 2011/2012/1 | 8/F         | 4   | F   | None             | Acute myocarditis     | Acute myocarditis          | B positive by rapid test         | Pericardial effusion with hypokinesis of LV wall | CPK 215                | Peramivir           | Steroid           | Not used         | Not used           | Improved |
| 2011/2012/2 | 6/M         | 3   | M   | Shock/day 3     | Acute myocarditis     | Acute myocarditis          | B positive by rapid test         | Hypokinesis              | CPK 736                | Oseltamivir          | Steroid           | Not used         | PCPS              | Not done |
| 2011/2012/3 | 10/F        | 2   | F   | Dyspnea day 2   | Acute myocarditis     | Acute myocarditis          | B positive by rapid test         | Pericardial effusion with hypokinesis of LV wall | CPK 13230           | Peramivir           | G-globulin       | Not used         | Not used           | Improved |

Table 1: Characteristics of pediatric myocarditis patients with influenza virus in 3 consecutive seasons in Japan

T/F s/s 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 cardio pulmonary support.

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 [1-3,7,18]. 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

1. JCS Joint Working Group (2011) Guidelines for diagnosis and treatment of myocarditis (JCS 2009): digest version. Circ J 75: 734-743.
2. Estabragh ZR, Mamas MA (2013) The cardiovascular manifestations of influenza: a systematic review. Int J Cardiol 167: 2397-2403.
3. Mamas MA, Fraser D, Neyes L (2008) Cardiovascular manifestations associated with influenza virus infection. Int J Cardiol 130: 304-309.
4. Bowles NE, Ni J, Kearney DL, Pauschinger M, Schultheiss HP, et al. (2003) Detection of viruses in myocardial tissues by polymerase chain reaction. evidence of adenovirus as a common cause of myocarditis in children and adults. J Am Coll Cardiol 42: 466-472.
5. Koide H, Kitaura Y, Deguchi H, Ukimura A, Kawamura K, Hirai K (1992) 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 56: 1081-1093.
6. Ukimura A, Izumi T, Matsunori A; Clinical Research Committee on Myocarditis (2011) Guidelines for diagnosis and treatment of myocarditis. JCS Joint Working Group (2011). Circ J 74: 2193-2199.
7. Ukimura A, Satomi H, Ooi Y, Kanzaki Y, Inomata T, Izumi T (2013) A national survey on myocarditis associated with influenza A (H1N1) pandemic in Japan. J Am CollCardiol 55: 928-929.
8. Ukimura A, Satomi H, Ooi Y, Kanzaki Y. (2012) Myocarditis Associated with Influenza A (H1N1) Pandemic in Japan organized by Japanese Circulation Society (2010) A national survey on myocarditis associated with the 2009 influenza A (H1N1) pandemic in Japan. Circ J 74: 2193-2199.
9. Weiss TW, Stensaeth KH, Ertlsland J (2010) Myocarditis in a juvenile patient with Influenza virus infection. Eur Heart J 31: 277.
10. Aoyama N, Izumi T, Hiramori K, Isobe M, Kawana M, Hiroe M, et al (2002) National survey of fulminant myocarditis in Japan: therapeutic guidelines and long-term prognosis of using percutaneous cardiopulmonary support for fulminant myocarditis (special report from a scientific committee). Circ J 66: 133-44.
11. Centers for Disease Control and Prevention (CDC) (2010) Patients hospitalized with 2009 pandemic influenza A (H1N1) - New York City, May 2009. MMWR Morb Mortal Wkly Rep 58: 1436-1440.
12. Kerkhove MDV, Vandemaele KA, Shinde V, Jaramillo-Gutierrez G, Koukounari A, et al. (2011) On behalf of the WHO Working Group for Risk Factors for Severe H1N1pdm Infection: Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. Pros Med. 7: 1-12.
13. The Ministry of Health, Labor, Tokyo, Japan: A National survey of influenza myocarditis patients in the last winter in Japan (in Japanese). April 1, 2011.
14. Sugaya N (2011) Widespread use of neuraminidase inhibitors in Japan. J Infect Chemother 17: 595-601.
15. Ikematsu H, Kawai N, Kashiwagi S. In vitro neuraminidase inhibitory activities of four neuraminidase inhibitors against influenza viruses isolated in the 2010-2011 season in Japan. J Infect Chemother. 2012; published online Feb.28
16. Pan HY, Yamada H, Chida J, Wang S, Yano M, et al. (2011) Up-regulation of ectopic trypsin in the myocardium by influenza A virus infection triggers acute myocarditis. Cardiovasc Res 89: 595-603.
17. Kotaka M, Kitaura Y, Deguchi H, Kawamura K (1990) Experimental influenza A virus myocarditis in mice. Light and electron microscopic, virologic, and hemodynamic study. Am J Pathol 136: 409-419.